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CYTOLOGIC EFFECTS OF THE LIGATION OF THE MAJOR BLOOD VESSELS OF THE KIDNEY OF THE ALBINO RAT¹

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Following the pioneer work of Litten,¹ Palma-Pollack,² Sacerdotti and Frattin,³ Poscharissky⁴ and Lick,⁵ Maximow⁷ confirmed the observation that vasoligation of the kidney in the rabbit results in the formation of bone, especially in the region of the renal hilus. Maximow extended the investigation and described in addition myeloid metaplasia in the subepithelial region of the pelvis. He claimed that the red cell ancestors of the ectopic bone-marrow are pluripotential small lymphocytes that have become entrapped in the capillaries. Though Maximow consistently regarded the large lymphocyte as potentially identical with the hemoblast, this is the only place in which he ascribes erythrocytopoietic potency via a large lymphocyte stage, to the small lymphocyte.

The primary object of our investigation was to test this conclusion by further experimental studies in this case with the albino rat. We succeeded in effecting osseous metaplasia in the renal hilus in some

¹ Submitted for publication, June 28, 1930.

² From the Laboratory of Histology and Embryology, Department of Medicine, University of Virginia.

¹ Litten, M. Untersuchungen über den hämorrhagischen Infarkt und über die Einwirkung arterieller Anämie auf das lebende Gewebe, Berlin, A. Hirschwald, 1879, ch. 1.

² Talmr, S. Der Verschluss der Nierarterien und seine Folgen, Ztschr. f. klin. Med. **2** 483, 1881.

³ Pollack, K. Beiträge zur Metaplasiefrage, Arb. a. d. path.-anat. Abteilung d. k. hyg. Inst. zu Posen, Wiesbaden, J. F. Bergmann, 1901, pp. 154-204.

⁴ Sacerdotti, C., and Frattin, G. Ueber die heteroplastische Knochenbildung, experimentelle Untersuchungen, Virchows Arch. f. path. Anat. **168** 431, 1902.

⁵ Poscharissky, J. F. Ueber heteroplastische Knochenbildung, eine pathologisch-histologische und experimentelle Untersuchung, Beitr. z. path. Anat. u. z. allg. Path. **38** 135, 1905.

⁶ Lick, E. Experimenteller Beitrag zur Frage der heteroplastischen Knochenbildung, Arch. f. klin. Chir. **80** 279, 1906.

⁷ Maximow, A. A. Experimentelle Untersuchungen zur postfotalen Histogenese des myeloiden Gewebes, Beitr. z. path. Anat. u. z. allg. Path. **41** 122, 1907.

instances, but as regards the erythrocytopoietic capacity of the lymphocyte under these conditions our results are definitely negative. However, in the course of this work data accrued concerning especially the migration of fibroblasts and macrophages, regenerative changes in the kidney, and the origin of plasma cells and Russell body cells, all of which appear to us deserving of record.

MATERIAL AND METHODS

The material consisted of sixty-eight left kidneys of albino rats. These kidneys were of four types: normal kidneys with the major blood vessels ligated at the hilus, kidneys with an injection of trypan blue in the renal artery, followed in some cases by ligation of the major vessels, and kidneys from animals on which splenectomy and vasoligation had been done. The kidneys were removed after ligation for twenty-four hours, three days and from one to ten weeks. On autopsy, the kidneys were fixed in Helly's Zenker-formaldehyde solution. Kidneys of more than three weeks' ligation were decalcified in 3 per cent nitric acid alcohol. The material was embedded in paraffin and sectioned at 6 microns. Some sections were stained with hematoxylin-eosin-azure II according to the method of Maximow as given by McClung,⁸ others, by the Foot silver technic for demonstration of reticulum. The unligated kidneys from the experimental animals, together with lymph nodes, spleen and bone-marrow, were fixed and stained in a similar manner. Wet smears were made from the cortices of kidneys at various stages of ligation. These were fixed and stained with hematoxylin-eosin-azure II according to the method of Bloom.⁹ Smears from kidneys ligated for one, two and six weeks, respectively, were studied after supravital staining with neutral red and Janus green according to the method of Sabin.¹⁰

Pathologic kidneys of man were studied for comparative purposes. These showed infarction, chronic passive congestion, parenchymatous degeneration, arteriosclerosis, lymphosarcoma, colloid degeneration, amyloid formation and acute glomerulonephritis.

OBSERVATIONS

As stated in the introduction, this series of experiments demonstrates that myeloid metaplasia does not follow ligation of the major vasa of the kidney of the albino rat. Thus the major thesis which these experiments sought to demonstrate following Maximow's claim for the rabbit, viz., that under conditions of relatively slow circulation entrapped lymphocytes may metamorphose into red blood corpuscles, is not verified. No appreciable number of lymphocytes were entrapped in the vasa of the kidney following the ligation. Such lymphocytes as appeared in our material came in from a collateral circulation secondarily established and appearing usually three weeks

⁸ McClung, C. Handbook of Microscopical Technique, New York, Paul B Hoeber, 1929.

⁹ Bloom, W. The Origin and Nature of the Monocyte, *Folia haemat* **37** 1, 1923.

¹⁰ Sabin, F. R. Studies of Living Human Blood Cells, *Bull. Johns Hopkins Hosp* **34** 277, 1923.

after ligation. These lymphocytes migrated out of invading lymphatics of the capsule and superficial cortical region, and in the cortex changed into plasma cells and large lymphocytes. The plasma cells in turn became Russell body cells but the large lymphocytes did not develop further. These cytologic changes began to occur during the third week of ligation and were progressively continuous throughout the experiments. The final picture of the ligated kidney in our series of experiments resulted from changes brought about by invading neutrophil granulocytes, fibroblasts, macrophages, blood vessels, lymphatics and lymphocytes. The striking feature in the majority of kidneys examined after the third day of ligation was the establishment of three independent zones: (1) a zone beneath the pelvic epithelium ("Rind-zone" of Maximow⁷ in the rabbit), (2) a cortical zone enclosed in a thick capsule and separated from the next zone by a band of neutrophil granulocytes and (3) a medullary zone. Changes in these three zones were independent of each other and varied with differences in the extent of the collateral circulation. In a brief description of the different zones we can more readily indicate wherein our results differ from those of Maximow.

In the first zone, that beneath the pelvic epithelium, there is in the normal kidney a thin layer of collagenous fibers and fibroblasts directly connected with the perineal tissue at the hilus. Internally, this layer extends to the base of the papilla and its boundary is crossed by the renal tubules which extend into the medulla from the more distal regions of the cortex. The larger vessels course in this tissue to reach the renal arcade. Following ligation the arteries of this region were collapsed, and the veins were distended with red blood corpuscles. The surrounding fibroblasts enlarged and deposited coarse collagenous fibers. New vasa penetrated this layer from the hilus. A new circulation was set up, and the distended old veins became filled with an organizing thrombus. Few lymphocytes were seen to be entrapped here. There was no picture at any time resembling the conditions described by Maximow in which, in this particular region, the entrapped small lymphocytes changed into large lymphocytes and the latter into megakaryoblasts that finally gave rise to erythroblasts, normoblasts and erythroplastids. There was definitely a highly vascular area here of recent origin and established by ingrowing vessels. In several kidneys, one each of the fourth, fifth and ninth week and two of the sixth week, of ligation, bone was present in this zone (fig. 1). Stages in the establishment of the bone by activity of the fibroblasts were observed. In this region of the rabbit's kidney Maximow found metaplastic bone-marrow, but we found none. The changes here were independent of changes in the other parts of the kidney.

In the second or cortical zone, two types of changes were observed following ligation. In the normal kidney, this zone is enclosed in a

thin capsule of fibro-elastic connective tissue. The cortex contains the glomeruli, convoluted tubules and collecting tubules. The tubules are separated from each other by narrow blood spaces lined with reticulum (fig 2 *A*). Only reticulum cells are found here, and these lie close against the homogeneous basement membrane of the tubules (fig 5 *B*). In this interpretation of the interstitial stroma of the rat's kidney, we agree with Corner¹¹. Fibroblasts are relatively scarce, and the blood



Fig 1—Vertical section through the pelvic mucosa of a kidney ligated for four weeks. Note the transitional epithelium of the pelvis on the left separated from the underlying metaplastic bone by a narrow layer of cellular connective tissue. Helly fixation, eosin-azure II, $\times 600$.

spaces are usually occupied by red blood corpuscles. Striking changes took place in this region following ligation. After ligation for twenty-four hours, the blood spaces were distended with red blood corpuscles and the tubules were pushed apart (fig 3 *A*). In this distended condition, the ramification of the reticulum net and the homogeneous base-

¹¹ Corner, G. W. On the Widespread Occurrence of Reticular Fibrils Produced by Capillary Endothelium, *Carnegie Inst., Contrib. Embryol.* (no 272) 9, 1920.

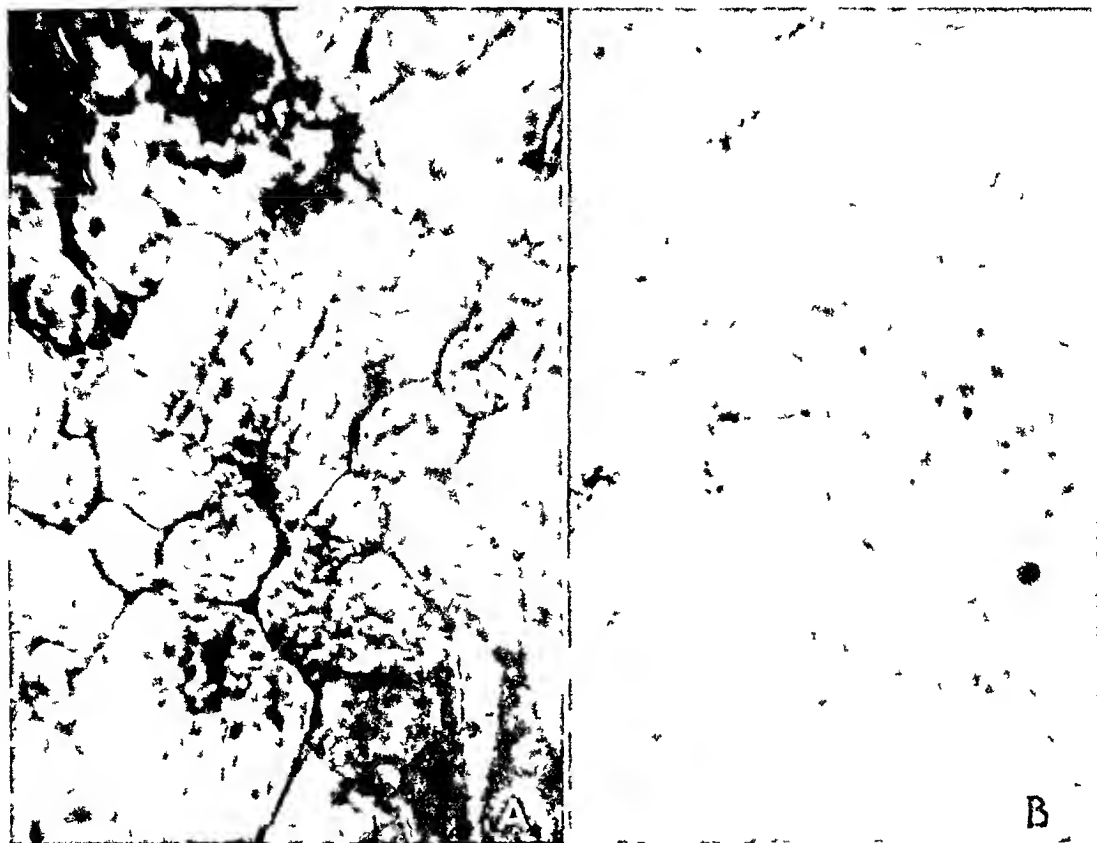


Fig 2—*A*, the cortex of the normal kidney of the albino rat. The reticulum between the tubules is black. *B*, the cortex of a normal kidney. Helly fixation, Foot reticulum technic for *A* and hematoxylin-eosin-azure II for *B*, $\times 350$

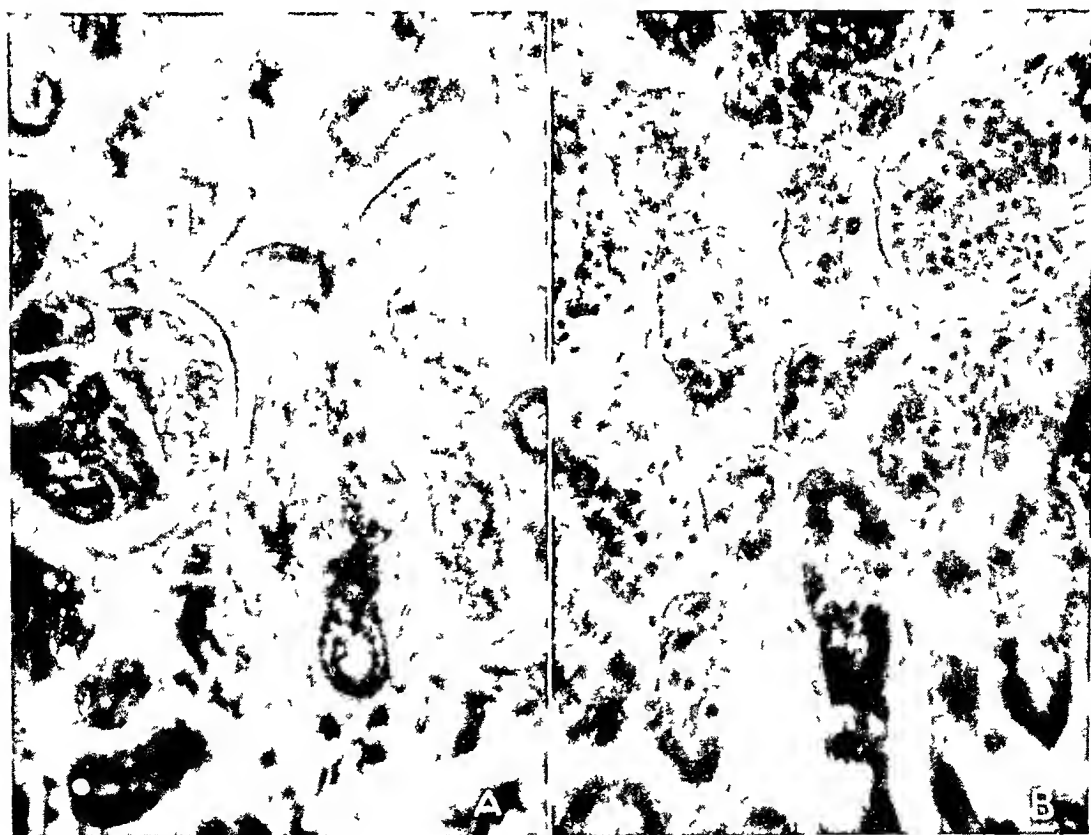


Fig 3—*A*, the cortex of a kidney ligated for twenty-four hours, *B*, for three days. Helly fixation, Foot technic, $\times 350$

ment membrane of the tubules and glomeruli could be distinctly observed. The renal epithelium was largely necrotic. After three days, the capsule began to thicken as the result of an increase in the number of fibroblasts and collagenous fibers, and there were accumulations of neutrophil granulocytes in the blood spaces nearest the cortex (fig 3 *B*). The neutrophil granulocytes seemed to be invading the cortex from the perirenal vasa. Fibroblasts, monocytes and macrophages were present between the tubules nearest the capsule (fig 4).



Fig 4—Drawing of a subcapsular region from the cortex of the kidney, after three days ligation. Note the fibroblasts and macrophages between the tubules, the macrophages within the tubules and the homogeneous remnants of the necrotic renal epithelium. Helly fixation, hematoxylin-eosin-azure II, $\times 1,350$.

The fibroblasts were large, and many of them were in mitosis. Usually, they lay with the long axis at right angles to the capsule, thus giving the impression of migration into the cortex. Macrophages characterized by a foamy cytoplasm were present within some of the more peripheral tubules (fig 5 *A*). These macrophages were evidently destroying the remnants of the tubule epithelium. Many of the macrophages were in mitosis. The reticulum framework was as clear as in the normal kidney. No collagenous fibers were present.

In most of the kidneys ligated for one week, the capsule was very thick and there was evidence of the beginning of a collateral circulation extending to the cortex from the perirenal vasa. In some kidneys, this was an extension of a branch of the inferior phrenic artery, and in others the collateral circulation arose from the splenic vessels. Fibroblasts, monocytes, macrophages, mast cells, neutrophil and eosinophil granulocytes, small lymphocytes and a few plasma cells lay between the collagenous fibers of the capsule. In the cortex, many of the tubules had disappeared, and their places were occupied by

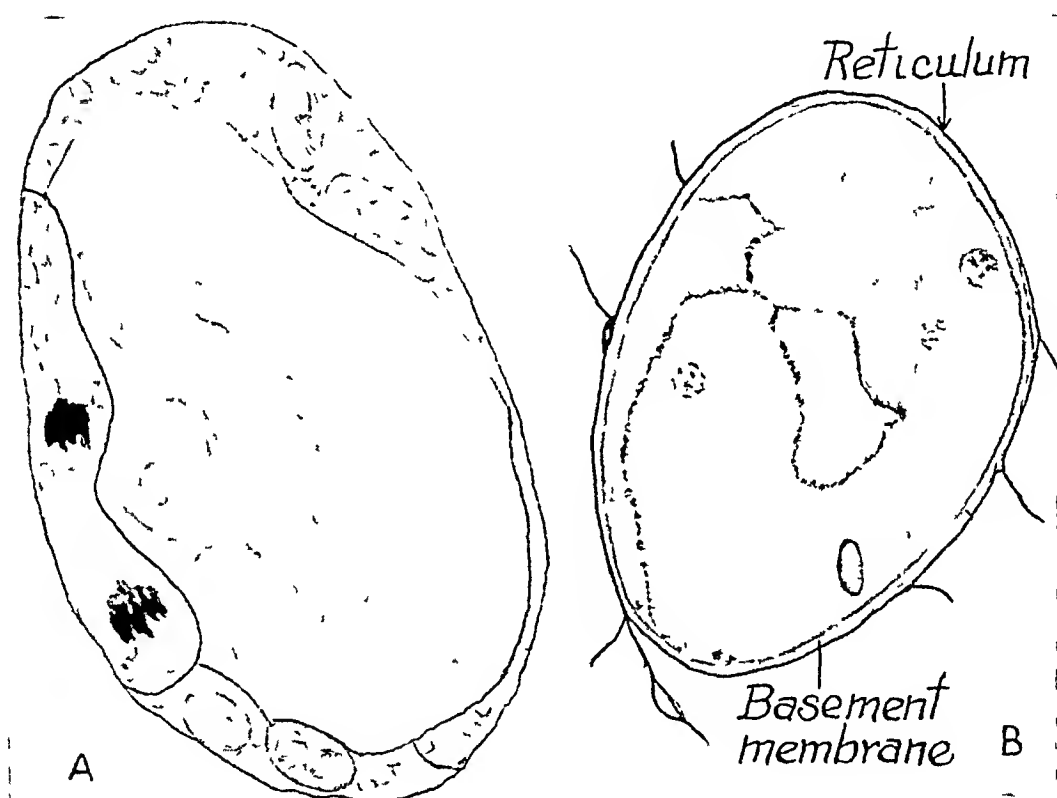


Fig 5—*A*, drawing of the cortex of a kidney after three days' ligation. Note the central necrotic renal epithelial remnants and the peripheral macrophages. One of the macrophages is in mitosis. *B*, drawing of a section of a tubule from the cortex of a kidney ligated for one week. Note the relation of the delicate reticulum fibers to the homogeneous basement membrane. Helly fixation, hematoxylin-eosin-azure II for *A* and Foot technic for *B*, $\times 1,350$

macrophages. In other regions, the tubules appeared as dull hyaline masses enclosed in a framework of reticulum (figs 5 *B* and 6 *A*). The neutrophil granulocytes observed in the periphery of the cortex at the end of the third day of ligation had now penetrated deeper. In some kidneys, they formed a layer about half way between the capsule and the medulla, in others, they had reached the corticomedullary boundary

The corticomedullary zone of neutrophil granulocytes was a distinct feature of practically all of the kidneys examined in the latest weeks of ligation. This zone separated an organizing neocortex from a necrotic, unorganizing medulla. The characteristic feature of the one week stage of ligation was the large size of the fibroblasts which filled the reticulum-lined spaces and which in a few places were surrounded by coarse collagenous fibers. From comparison of these in position and number with fibroblasts in the earlier stages of ligation, it was concluded that

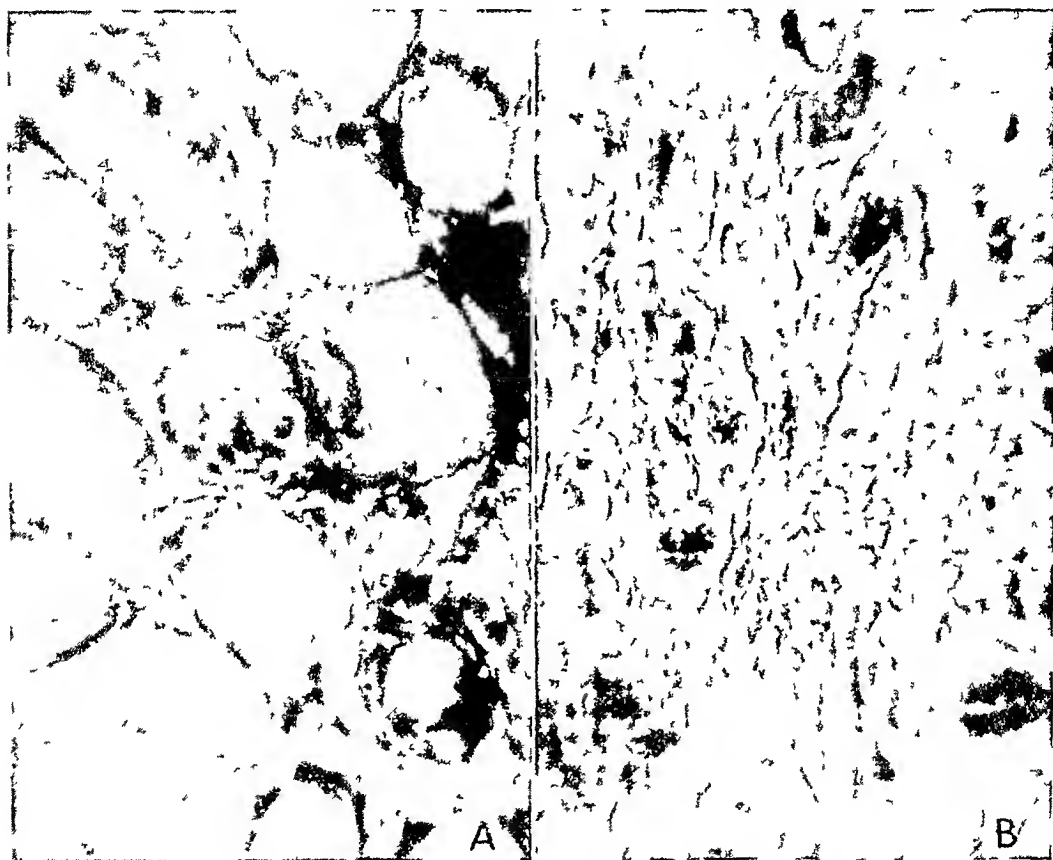


Fig 6—*A*, the cortex of a kidney ligated for one week, *B*, for two weeks. Helly fixation, Foot technic, $\times 600$

they were derived from fibroblasts which had invaded the interstitial tissue from the capsule, and that they did not arise from preexisting interstitial cellular elements. Furthermore, fibroblasts were distinct from macrophages, and no transition from one type to the other could be recognized.

The conditions following the second week of ligation were similar to those following the first, except for more collagenous fibers and more extensive replacement of tubules by macrophages (fig 6*B*). Few tubules had the appearance of calcification, a feature characteristic of the tubules of the ligated kidney of the rabbit following one week of ligation.

tion (Mannow¹⁰). The vasa present in the capsule of the kidney ligated for one week were represented in the kidney after two weeks' ligation by intracortical sprouts. The endothelial cells of these invading vasa were very large and were similar to the endothelial cells of the vasa that invade granulation tissue. There was no evidence that they became free and transformed into macrophages.

After two weeks' ligation and during the preceding stages, in kidneys into which trypan blue had been injected before ligation,

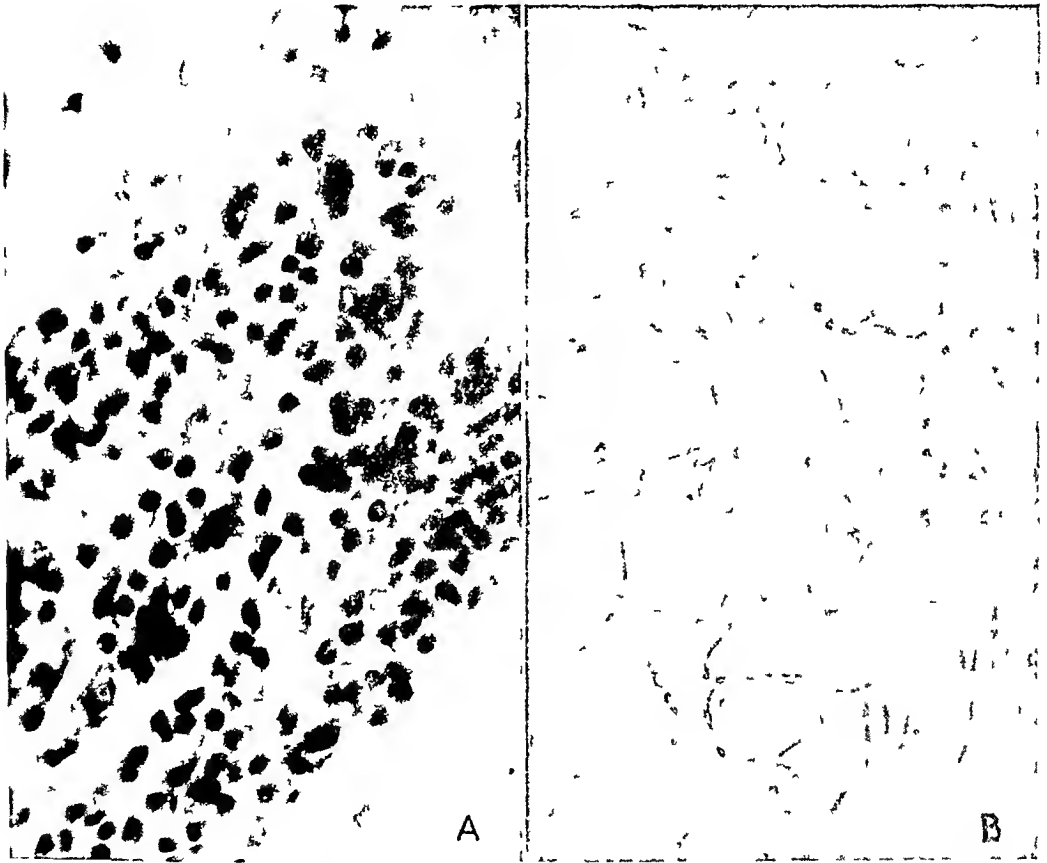


Fig 7—*A*, the cortex of a kidney ligated for three weeks $\times 600$, *B*, for four weeks. Helly fixation, hematoxylin-eosin-azure II, $\times 350$.

there was no indication that any of the interstitial elements were phagocytic. The trypan blue, when observed, was usually stored in the necrotic renal epithelial cells. The kidneys into which trypan blue had been injected and which had then been ligated and the simple ligated kidneys underwent the same type of modification. The invading fibroblasts, macrophages and vasa all stopped at the corticomedullary zone of neutrophil granulocytes. In this zone, the reticulum fibers had largely disappeared. Fibroblasts and macrophages apparently had no destructive effect on the reticulum fibers, but it seemed as though they might be digested by neutrophil granulocytes.

These same processes of increase in number of fibroblasts and macrophages, collagenous deposition and tubular replacement were present in the kidneys following the third week of ligation. In addition, lymphatics that to this time were not apparent in the cortex became visible by reason of distention with small lymphocytes (fig 7A). They were just beginning to grow into the cortex from the capsule. The question arises as to whether they were lymphatics originally present which had become filled with lymphocytes because the normal egress through the hilus was lacking, or whether they were neoformations. From what is known of the course of the lymphatics through the kidney it would seem that the ligation of the vasa would have blocked the lymph flow and entrapped the lymphocytes. If this had been the case, however, we would expect the lymphatics to have been blocked immediately following ligation. Since there was no evidence of this, we interpret the lymphatic channels that appeared beginning with the third week of ligation as neoformations. In the region of the lymphatics were many free extravascular small lymphocytes, transition stages from small lymphocytes to large lymphocytes and to plasma cells. Transition stages between plasma cells and Russell body cells were also present. The Russell body cells were characterized by the cartwheel type of nucleus of the plasma cell and a cytoplasmic content of one or more eosinophil masses of various shapes (fig 10A). From the sequence of changes described, the Russell body cells may be regarded as the end-cells of lymphocyte degeneration. They usually passed through the plasma cell stage first, but some cells resembling small lymphocytes contained the characteristic Russell bodies.

In most of the kidneys of the four week stage of ligation, the conditions of the three week stage were characteristic, with an increase of fibroblasts, collagenous fibers, lymphatics, lymphocytes, plasma cells, Russell body cells and macrophages. In one kidney, however, there was apparently little change in the cortex from that of the normal unligated kidney, except for necrosis of the tubules. These were colorless epithelial shells between which could be seen the reticulum cells and fibers (fig 7B). None of the changes characteristic of the other kidneys had taken place. A few macrophages were present at one end of the cortex near the hilus. The explanation for this apparent static condition lay in the failure of development of a neocortical circulation. This in turn may have brought about the failure of invasion of the cortex by neutrophil granulocytes. From a study of our whole series, the neutrophil granulocytes seem to have been stimulators of further change as regards fibroblasts, macrophages and invading vasa. The static condition found here may have persisted because of the lack of an initial stimulus for change.

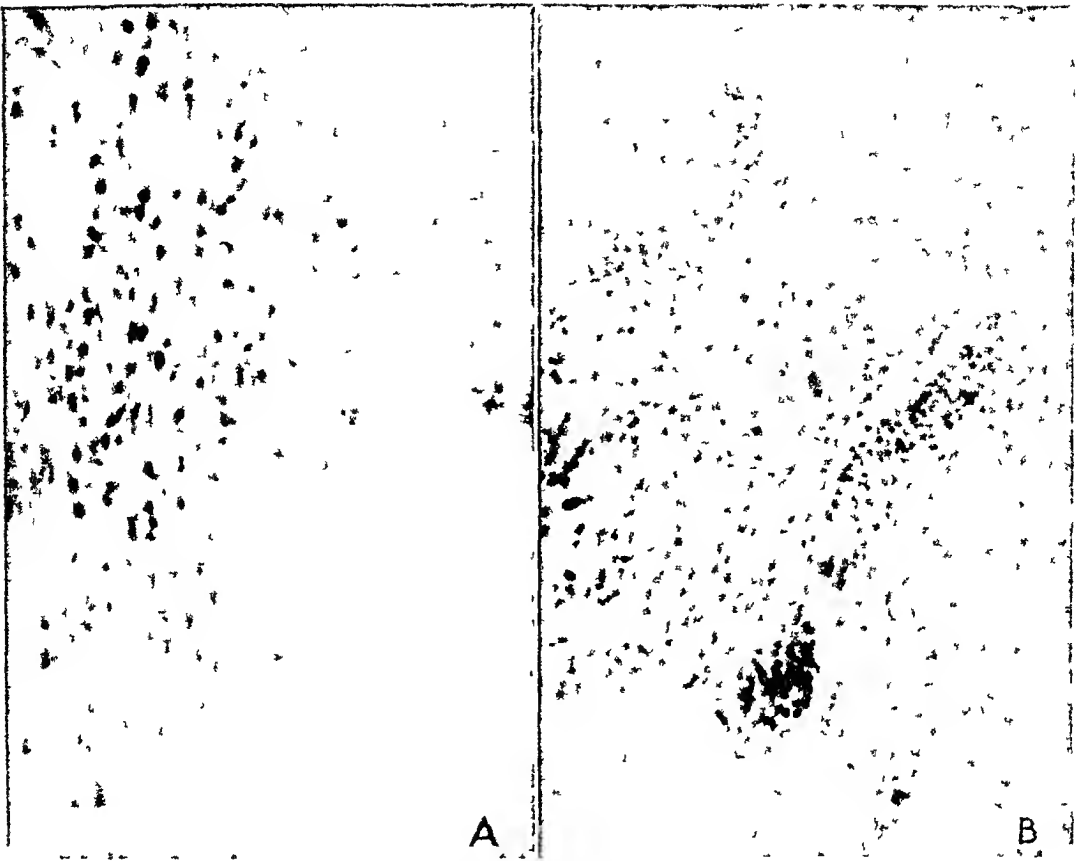


Fig 8—*A*, the cortex of a kidney ligated for seven weeks, *B*, for eight weeks Helly fixation, hematoxylin-eosin-azure II, $\times 350$

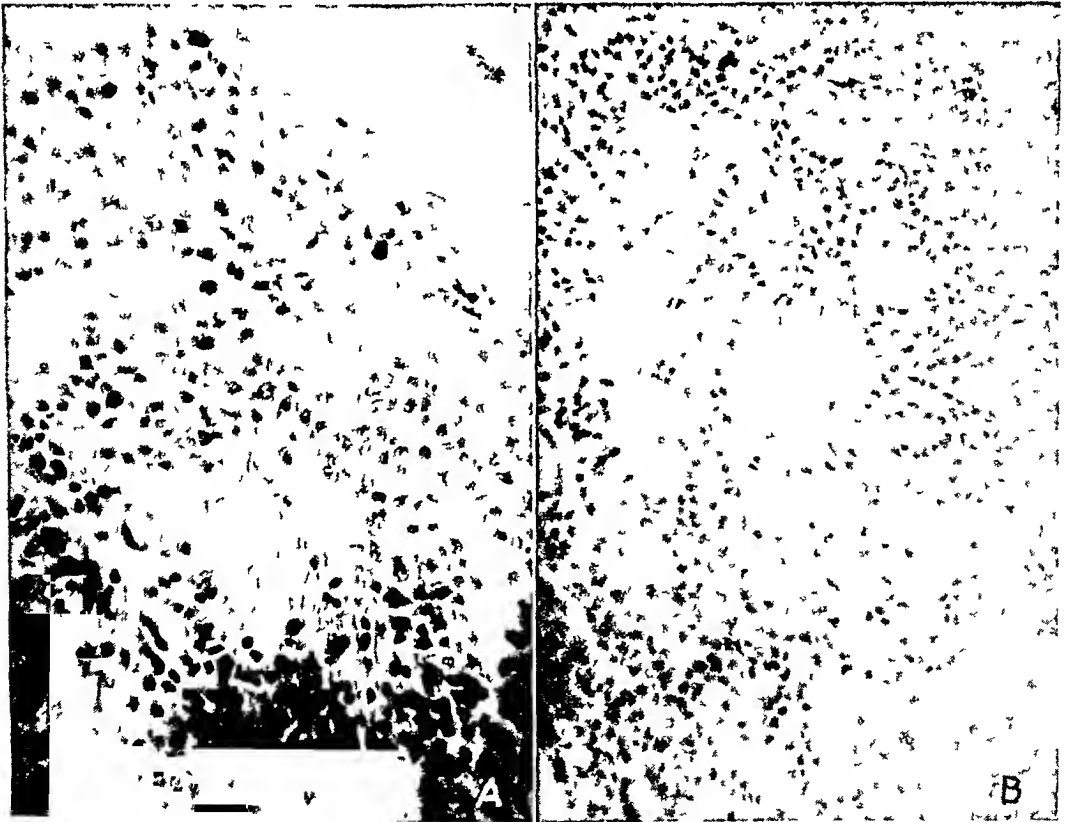


Fig 9—*A*, the cortex of a kidney ligated for nine weeks $\times 500$, *B*, for nine weeks Helly fixation, hematoxylin-eosin-azure II, $\times 350$

Beyond the four week stage, up to and including the ten week stage, most of the kidneys examined showed progressive fibrosis (figs 8A to 9B), replacement of tubules, flooding of the fibrous tissue with lymphocytes, transition stages between small lymphocytes and plasma cells and large lymphocytes, and between plasma cells and Russell body cells. Russell body cells present in a kidney of eight weeks' ligation contained inclusions with great diversity of shape (fig 10A). In contrast with the large eosinophil inclusions characteristic of the Russell body cells were the small eosinophil globules present in certain plasma cells (fig 10B). This type of plasma cell in which the cytoplasm was filled with small eosinophil globules has been called the eosinophil plasma cell by Dubreuil and Favie¹²

Although the majority of kidneys in the later weeks of ligation showed these changes, some of them remained completely unchanged as regards regenerative organization. The capsule was thin, the tubules were present occupying the same amount of space as in the unligated kidney, and the intertubular stroma remained unchanged. In such kidneys, some of the tubules were calcified and appeared as shiny eosinophil or basophil masses in the eosin-azure II preparations.

The third zone of the kidney affected by ligation was the medulla. This zone includes the papilla, as well as the medullary portion at its base. In the kidneys of the earlier stages of ligation, this region was merely a necrotic mass cut off from the rest of the kidney by the corticomedullary zone of neutrophil granulocytes. The remnants of the necrotic renal epithelium were visible within the meshes of the reticulum framework, but there was little or no replacement of these tubules by macrophages. Few neutrophil granulocytes were present in the blood spaces, and usually the whole medullary mass showed shrinkage after the first week. This shrinkage went steadily on until the tenth week, then the kidney was much smaller than its original size and the medulla occupied only a small central portion. As late as eight weeks following ligation, the necrotic medulla could be readily shelled out of the fibrous cortex on hardening. The fibrosis which took place in the cortex had apparently not invaded the medulla.

A series of experiments was made to see whether the extirpation of the spleen would have any effect on the changes in the ligated kidney. Kidneys from animals of this series showed no differences from those of the simple ligation, except possibly an increase in the amount of lymphoid tissue in the cortex.

12 Dubreuil, G, and Favre, M. Cellules plasmatiques. Plasmazellen a granulations spécifiques. Cellules a corps de Russell (cytologie et formes évolutives), Arch d'anat. micr **17** 302, 1921

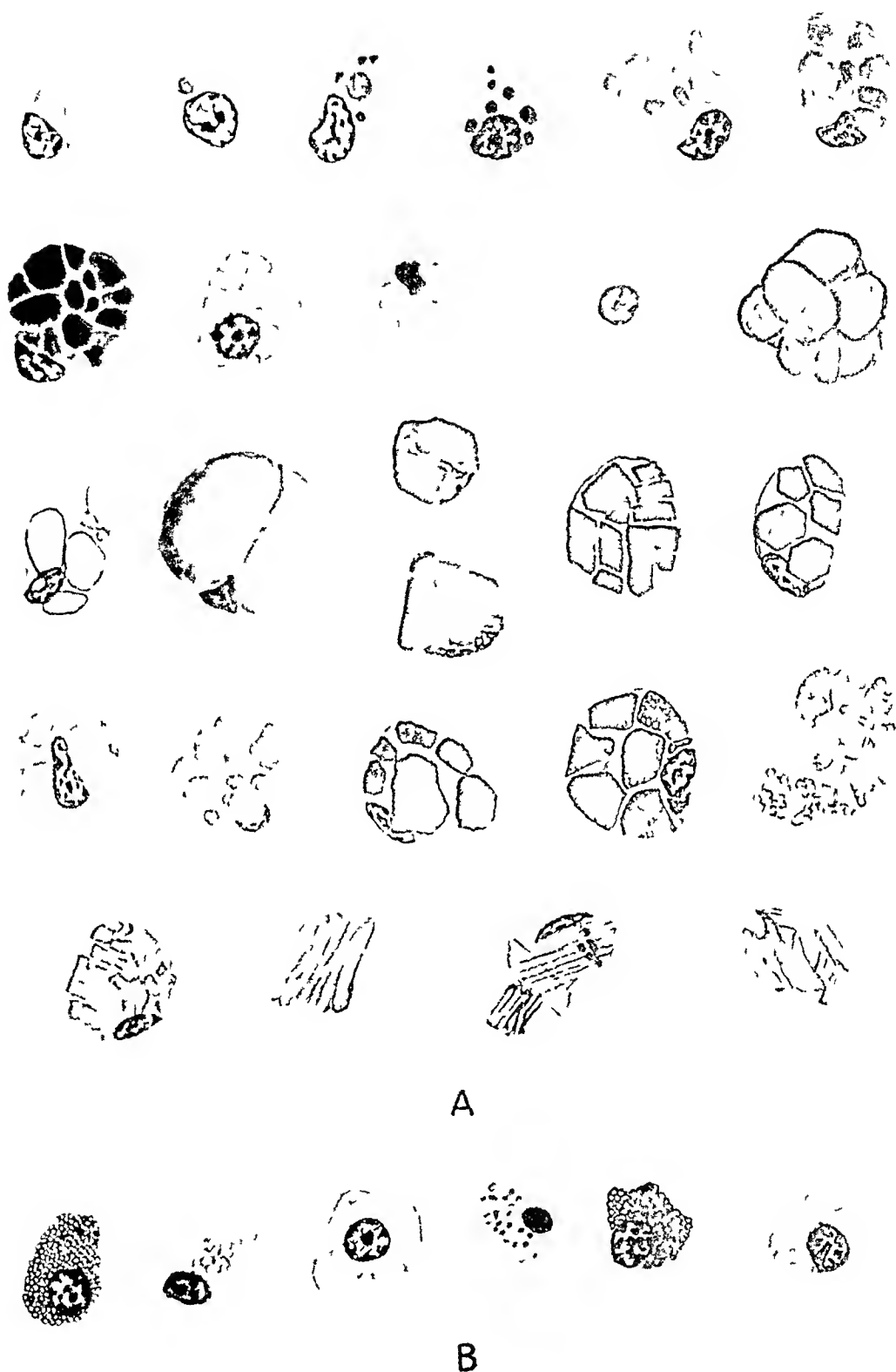


Fig 10—*A*, drawings of various types of Russell body cells from the cortex of a kidney ligated for eight weeks. The inclusions are eosinophil in reaction. The depth of the ink indicates the degree of tinctorial (red) reaction. *B*, drawings of plasma cells with eosinophil inclusions. Note uniformity of size and complete filling of cytoplasm with globules as compared with the arrangement of the inclusions of the Russell body cells. Helly fixation, hematoxylin-eosin-azure II, $\times 1,350$

COMMENT

In these experiments, we failed to find in the ligated kidney of the rat a series of changes comparable to those described by Maximow⁷ for the rabbit. The changes most like those described by Maximow were those leading to the formation of bone in the subepithelial layer of the pelvis. However, no myeloid tissue accompanied this bone. Under no circumstances were small lymphocytes observed to change into hemoblasts. Since no areas of entrapped lymphocytes were found following ligation, all the lymphocytes occurring in the stroma of the kidney in the later stages of ligation were considered to be migrants from invading lymphatics. Stages between small lymphocytes and large lymphocytes were readily seen, as were transition stages between small lymphocytes and plasma cells. From the conditions found here it would seem that the plasma cells are degeneration phases of small lymphocytes. The plasma cells themselves become modified into Russell body cells and eosinophil plasma cells. From the shrunken appearance of the nuclei of the Russell body cells it is concluded that they are stages in the degeneration of plasma cells. Such a conclusion disagrees with the claim of Dubreuil and Favre,¹² who as a result of their observations on the Russell body cells in the omentum of the rabbit stated that the Russell body cells are possibly secretory cells of the rhagiocin type. Our conclusion as to the degenerate nature of the Russell body cells is further strengthened by the sequence of events leading to their appearance in the cortex of the ligated kidneys, the general pyknotic character of their nuclei and the diversity in the shape of their inclusions. The inclusions appeared to be the result of the resorption of some substance from the surrounding tissue, which gradually increased in amount, and which was deposited in the cell in more or less crystalline form.

There was no evidence in our material for the view held by Maximow that some of the lymphocytes change into polyblasts. The cells that we call macrophages and consider comparable to the polyblasts of Maximow were all of extra renal origin, either from monocytes or tissue macrophages. We are in agreement with the view of Maximow that the fibroblasts and macrophages are distinct entities, at any rate so far as they occur in ligated kidneys. From the earliest appearance of macrophages and fibroblasts, these two series of cells took distinct parts in the changes in the cortex of the ligated kidney. The fibroblasts extended between the tubules and deposited a collagenous matrix. The macrophages invaded the tubule remnants and digested them, thereafter remaining as occupants of the reticulum outlining the shape of the tubules.

The conditions that were present in the ligated kidney at the end of the first week were much like those in experimental lesions of the

liver of the rat as described by Higgins and Murphy¹³. The necrotic area was walled off by a zone of neutrophil granulocytes, outside of which was a layer of macrophages. Higgins and Murphy concluded that in the liver the macrophages arose from two sources: the agranulocytes of the blood stream and the local histiocytes of the periportal tissue including detached Kupffer cells. In later stages, the enclosing wall contained fibroblasts, which they concluded were transformed macrophages developed largely from Kupffer cells. In our material, the history was clear that the macrophages were entirely distinct from the fibroblasts throughout the whole experimental series. Beginning with the third day following ligation, the macrophages and fibroblasts invaded the kidney from the capsule. Each had its own function. The macrophages cleared away debris and replaced the tubule cells, the fibroblasts followed along the reticulum lined spaces and deposited collagenous fibers between the reticulum fibers. There was no evidence in our material that the macrophages had a later history comparable to that described by Higgins and Murphy for the lesions of the liver. Of particular interest was the border of polymorphonuclear granulocytes that persisted between the necrotic medulla and the cortex and the similar wall of such cells around the lesion in the liver. In the liver they lay first in the lesion and gradually cleared it to take up positions on the margin of the necrotic area, but in the kidney they hardly ever penetrated the medulla.

Following ligation in the rabbit's kidney most of the tubules of the cortex early became calcified (Maximow⁷). There was little calcification in the kidneys in our material. Any explanation of this difference in two apparently similarly constructed kidneys would be merely a guess, unless the chemical conditions accompanying the stages of ligation were available.

The experimental conditions established here following ligation compare with conditions of infarction in the human kidney. Morphologically, the cortex of the rat's kidney on ligation is invaded by one large infarct. The degree of repair and replacement of the renal tissue depends on the reactions of the surrounding structures, particularly the collateral circulation. Infarcts in the kidney of man are usually limited to isolated regions and are produced by emboli in the branches of the renal arcade. Also, it seems important to note that they are most frequently found in the cortex only, and there end centrally at the border of the cortex and medulla. This is exactly the relation of the infarct in the rat's kidney. In the case of the renal infarct of man, when replacement occurs the process is initiated by autolysis of the tubules, and the area of infarction is invaded by poly-

¹³ Higgins, G. M., and Murphy, G. T. I. Experimentally Induced Localized Inflammatory Reactions in the Liver, *Arch. Path.* **9**: 659, 1930.

mononuclear granulocytes According to Wells,¹⁴ the leukocytes set free a substance called trephine which reacts on the surrounding tissues, particularly macrophages, fibroblasts, endothelium and lymphocytes The initiation of such changes begins in the kidney of the rat following the third day of ligation When the polymorphonuclear granulocytes begin to enter the kidney stroma, and after they have accumulated in large numbers at the corticomedullary boundary, the trephines presumably set free react on the other labile tissues and facilitate a gradual replacement of the whole mass by granulation tissue The kidney gradually becomes smaller as the fibrous organization proceeds, so that by the end of the tenth week the kidneys are merely small fibrous, lymphoid masses

Such an explanation of the replacement of the cortex by granulation tissue fails, however, to explain the persistence of the necrotic medulla Why do the neutrophil granulocytes fail to penetrate the medulla? In answer, one might suggest that the autolytic process is not strong enough there to attract them And if the neutrophil granulocytes do not enter the medulla, then the other elements that are considered to be influenced by the neutrophils do not progress beyond the corticomedullary boundary

In addition to the cytologic changes in the kidney, we wish to call attention to the demonstration in our preparations of the renal basement membranes In the normal kidney, stained with the Foot technic for the demonstration of reticulum, the reticulum fibers lining the intertubular capillaries are sharply evident (fig 2A), but the homogeneous basement membrane shown by Mall¹⁵ to be coexistent with the reticulum is not clear However, after ligation for twenty-four hours or more, as long as tubular remnants persist, the homogeneous band that extends around the periphery of the tubules between the renal epithelium and the reticulum is conspicuous (fig 5B) On necrosis of the tubules, the renal epithelial cells shrink away from the basement membrane, which in the Foot preparations appears as a pinkish band This membrane also covers the surface of the glomerulus The membrane persists for some time after necrosis of the tubules, indicating that it is of a nature different from the renal epithelial cells From its reaction in the silver preparations counterstained with van Gieson's picric acid-acid fuchsin solution this membrane appears to be of a collagenous nature

The study of the material by the method of supravital staining with neutral red and janus green was undertaken to see whether we could

14 Wells, H G Chemical Pathology, ed 5, Philadelphia, W B Saunders Company, 1925

15 Mall, F P Note on the Basement Membranes of the Tubules of the Kidney, Bull Johns Hopkins Hosp 2 133, 1901

discriminate between the globules of the macrophages and those of the Russell body cells. The globules were red, yellow or uncolored. Since these color differences mean merely differences in the hydrogen ion concentration, we could not make color discrimination between the globules of macrophages and Russell body cells. Many of the macrophages showed the characteristic petaloid pseudopodia. Engulfed materials, such as neutrophil granulocytes and effete red blood corpuscles, were more readily seen in the macrophages under supravital treatment than in the fixed material.

SUMMARY

Ligation of the major blood vessels of the kidney of the albino rat for a period of ten weeks is not followed by ectopic formation of bone-marrow.

Intramembranous bone may occur in the subepithelial connective tissue of the renal pelvis after four weeks' ligation.

The sequential pictures in the renal cortex following vasoligation are as follows: necrosis of renal tubules (in twenty-four hours), invasions of the cortex by neutrophil granulocytes from the capsular vasa (in three days), progressive replacement of the renal tubules by macrophages (in from one to ten weeks), progressive replacement of the renal capillaries by fibroblasts and collagenous tissue (in from one to ten weeks), persistence of the endothelial reticulum for eight weeks until completely obliterated by collagenous fibers, invasion of the fibrous neocortex by blood vessels (beginning at one week), invasion of the neocortex by lymphatics (beginning with the third week), migration into the fibrous neocortex of small lymphocytes and then metamorphosis into large lymphocytes and plasma cells (beginning with the third week), degeneration of plasma cells into Russell body cells (beginning with the fourth week), and isolation of the medulla from the cortex by a corticomedullary zone of neutrophil granulocytes (beginning with the first week).

Splenectomy synchronous with vasoligation does not effect changes different from those caused by simple ligation.

Kidneys into which trypan blue is injected before ligation show changes similar to those following simple ligation.

The renal intertubular capillary system is lined with a reticulum membrane that is separated from the renal epithelium by a homogeneous basement membrane, possibly collagenous. This membrane is more resistant to necrosis than the renal epithelial cells.

HUMAN URETER WITH STRIATED MUSCLE AND CILIATED EPITHELIUM †

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In order to amplify the slide collection used by students engaged in the study of normal histology, a resident pathologist of the Philadelphia General Hospital, at our request, excised about an inch of a grossly normal ureter from a recently dead adult cadaver and placed it in formaldehyde fixative. As he supposed that the material was to be used for histologic purposes only and that its freshness and good fixation were matters of prime importance, no memorandum was made by which it was subsequently possible to identify the body from which the tissue was removed, nor can the pathologist, who collected various tissues for various persons and for various purposes that same afternoon, now remember. The routine histologic studies of the necropsy material of about that date have not, however, revealed other anomalies.

The fragment of ureter, having been duly sectioned, proved to be exceptionally interesting in that it presented an anomaly of histologic structure that, so far as we have been able to determine, has not heretofore been observed. Indeed, a careful examination of the literature has failed to discover any mention of histologic anomalies of the ureter.

OBSERVATIONS

The Muscular Coats—There was a complete absence of the usual (normal?) unstriated muscle, its place being taken by perfectly striated fibers. These were arranged in three separate layers: (1) an inner layer, composed of fibrillar connective tissue and a few muscle fibers, in which the direction of the fibers was uncertain, different fasciculi seeming to run in different directions, mostly obliquely, though rather circumferentially than longitudinally, (2) a middle layer, circumferential in disposition, and made up of beautiful parallel fibers, of which the transverse striations and peripheral nuclei were distinct, and (3) an outer layer of longitudinal fibers, also of the striated variety.

* Submitted for publication, June 30, 1930.

† From the McManes Laboratory of Pathology, University of Pennsylvania, and the Woman's Medical College of Pennsylvania.

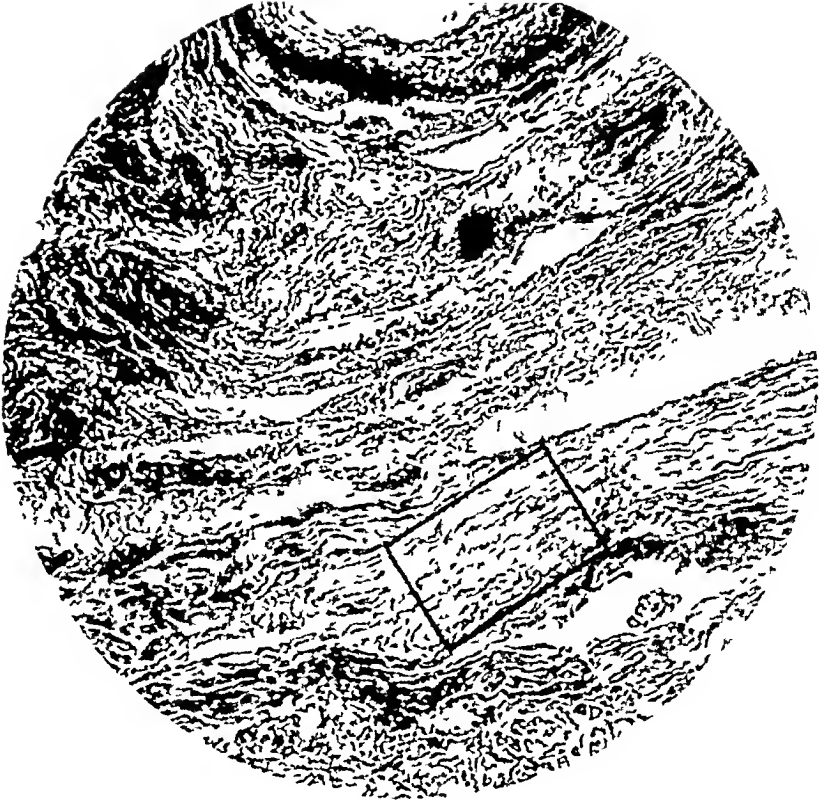


Fig 1—Section showing the entire thickness of the ureter with all of its coats
The inked oblong shows the field selected for the higher magnification shown in
the next illustration

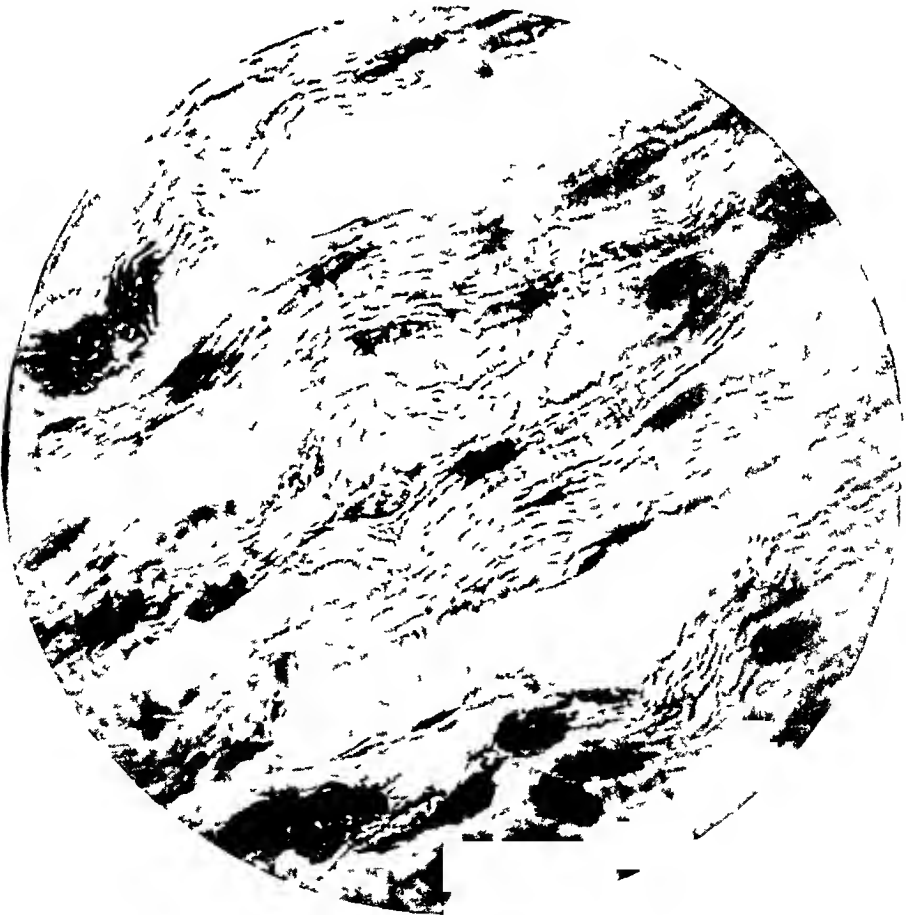


Fig 2—The cross-striations and peripheral nuclei are typical of the muscle
tissue in this peculiar ureter

It may be seen that the distribution and arrangement of the layers were unusual, and if Kolliker is right that the middle coat occurs only near the bladder, it may be assumed that the portion of the ureter examined must have been taken from the lower part of its course

The Mucosa—The epithelial lining was composed of stratified squamous cells unlike the normal urothelium. There was a distinct basal layer surmounted by from half a dozen to a dozen layers of cells, which, like those of the mucosa of the mouth, gradually flattened into



Fig 3—High power magnification of islet of ciliated columnar epithelium in the lining of the ureter

scales that desquamated. But there were exceptions, for in many places, usually of limited extent, the cells did not flatten, but after passing upward through a varying number of successive layers of polyhedral cells with pale cytoplasm, unexpectedly turned into columnar cells with ovoid nuclei at the bases, highly polychromatophilic cytoplasm and perfectly formed long cilia.

The discontinuousness of the columnar epithelium was interesting. As the section was moved on the stage of the microscope so as to follow the wavy line of the rugose mucosa, a long stretch with flattening cells

was suddenly interrupted by a group of perhaps a half dozen ciliated columnar cells, then another long stretch, with flattened cells, and then again a dozen or more ciliated columnar cells, and so on.

The photomicrographs accompanying this brief report show what has been described.

The explanation of the anomaly is extremely difficult. Suppose that in early embryonal life the ureters instead of having budded from the sides of the urogenital sinus, as they usually do, started at about the point of insertion of the wolffian ducts, as they frequently do, or from the lower part of the wolffian ducts themselves, as it is thought that they may do, then it is conceivable that in their upward extension they may have carried enough cells of the wolffian ducts for these to have survived the embryonal period and to have descendants even into adult life.

But our attempts to explain the presence of the striated muscle in the wall of this ureter have failed because our acquaintance with embryology is inadequate to furnish any clue.

FETAL ADENOMA OF THE HYPOPHYSIS AND DERMOID CYST OF THE HYPOTHALAMUS *

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The hypophysis and the adjacent tissues are the site of a great variety of tumors. The hypophysis itself is composed of several elements, and each is the potential anlage of a separate type of neoplasm. The pars nervosa gives rise to gliomas and the pars glandularis to simple hyperplasias, adenomas and carcinomas of many kinds. Even the dubious pars intermedia has been credited with certain tumors. Each of the cellular elements in the pars anterior has its special prototype in neoplasms. Thus, hypophyseal tumors have been described, composed entirely or chiefly of eosinophil cells, basophil cells, principal cells, "transitional cells" (Kraus¹), pregnancy cells and rarely even fetal indifferent cells. All possible combinations of these cells may be seen in the mixed adenomas, and in a single hypophysis two or more varieties of these tumors may be separately found. The relative frequency of the various types of tumor is roughly proportional to the relative numbers of the type cells. Thus, eosinophil adenomas are the most common, fetal cell adenomas are very rare, and pars intermedia tumors practically never occur in man.²

The tissues adjacent to the hypophysis are also the apex of several embryologic infoldings which leave behind them congenital rests of all kinds. Each such rest retains part or all of the potentialities of embryonal cells and may subsequently differentiate into tumors of the greatest variety and complexity of structure. These vary all the way from simple squamous epithelial cysts to teratomas and even to double monsters.

Besides the inclusion tumors from oral epithelium or external epithelium, other tumors, such as those that may be found elsewhere in the brain, may also appear in the hypophyseal area. These may be endotheliomas from the meninges, gliomas and neurocytomas from the cerebral substance or papillomas from the choroid plexus of the third

* Submitted for publication, June 30, 1930

* From the Department of Pathology of the Cook County Hospital

1 Kraus, E. J. Die Beziehungen der Zellen des Vorderlappens der menschlichen Hypophyse zu einander unter normalen Verhältnissen und in Tumoren, *Beitr. z. path. Anat. u. z. allg. Path.* **58** 159, 1914

2 Kraus, E. J., in Henke and Lubarsch. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer 1926, vol. 8

ventricle In this area, even these tumors, however, acquire a special significance beyond that which they possess in other parts of the brain They assume special pressure relationships to the cranial nerves, particularly the optic nerve The hypophysis and the hypothalamus are centers for the physiologic control of many important visceral functions Tumors in this region, by destroying one structure or another, produce specific depletion symptoms and permit some insight into the special functions of the various parts of the hypophyseal area

In the course of autopsy at the Cook County Hospital on two clinically obscure cases, two unusual types of tumor of this region were found One was a rare tumor of the hypophysis itself The other belonged to the group of inclusion tumors of the hypophyseal region and apparently was responsible for certain disturbances in visceral functions The description of these cases is warranted as a matter not so much of recording rare tumors, as of calling attention to several much mooted problems in the anatomy embryology and pathology of this area

REPORT OF CASES

CASE 1—Clinical History—Late one evening, a poorly nourished white man, 46 years old, was admitted to the neurology service He was extremely ill and semistuporous, so that his history was obtained from him with difficulty For two years he had been suffering from intermittent attacks of dull, aching pain in the right hypochondrium There had been considerable vomiting, and he had lost 70 pounds (31.8 Kg) in weight In the last three days, he had suddenly found himself getting stiff in both upper and both lower extremities He was soon unable to walk because of the marked spasticity

Physical Examination—Heart, lungs and abdomen were normal, except for tenderness in the right hypochondrium There was poor visual acuity The pupils were equal and regular, but reacted sluggishly to light and in accommodation The cranial nerves were normal The abdominal reflexes were absent The knee jerk was absent on the left side, but exaggerated on the right No pathologic reflexes were obtained Sensation was dulled over the entire body, and the patient's mentality was clouded Lumbar puncture yielded a cerebrospinal fluid that was clear and normal

Diagnosis—The patient died early the next morning, less than twelve hours after admission It was impossible to make a definite diagnosis in this brief time, but it was ventured as carcinoma of the stomach with recent cerebral metastases

Postmortem Examination (by Dr R. H. Jaffe)—At autopsy, the cause of the abdominal distress was found in a chronic peptic ulcer of the stomach, with marked stenosis of the pylorus The stomach was markedly dilated with about 1,500 cc of fluid Its mucosa showed distinct rugae, the "état mamelonné" of chronic gastritis The pylorus was the site of an oval ulcer, 7 by 3 mm in diameter, with a smooth floor and sloping edges The adjacent mucosa was pulled in toward it in the form of a healing, contracting scar The pyloric ring was narrowed so that it had a lumen of only 8 mm Supporting the suspicion of death in alkalosis were heavy calcium deposits in the tubular epithelium of the kidneys No calcium was found, however, in any of the other tissues

In removing the brain, the hypophysis was seen to bulge from the sella into the interpeduncular space. It was covered on its superior aspect by the tightly stretched operculum sellae. The hypophysis could be easily peeled out of the sella, and it was surrounded by an intact capsule. It was 30 mm in transverse, 23 mm in anteroposterior, and 22 mm in longitudinal diameter. The sella itself was wide and flat, 32 by 25 mm in diameter and 10 mm deep. Its internal surface showed no erosion.

The optic chiasma did not seem to be affected by the bulging of the hypophysis. The tracts were of normal size, shape and structure. Neither the peduncles

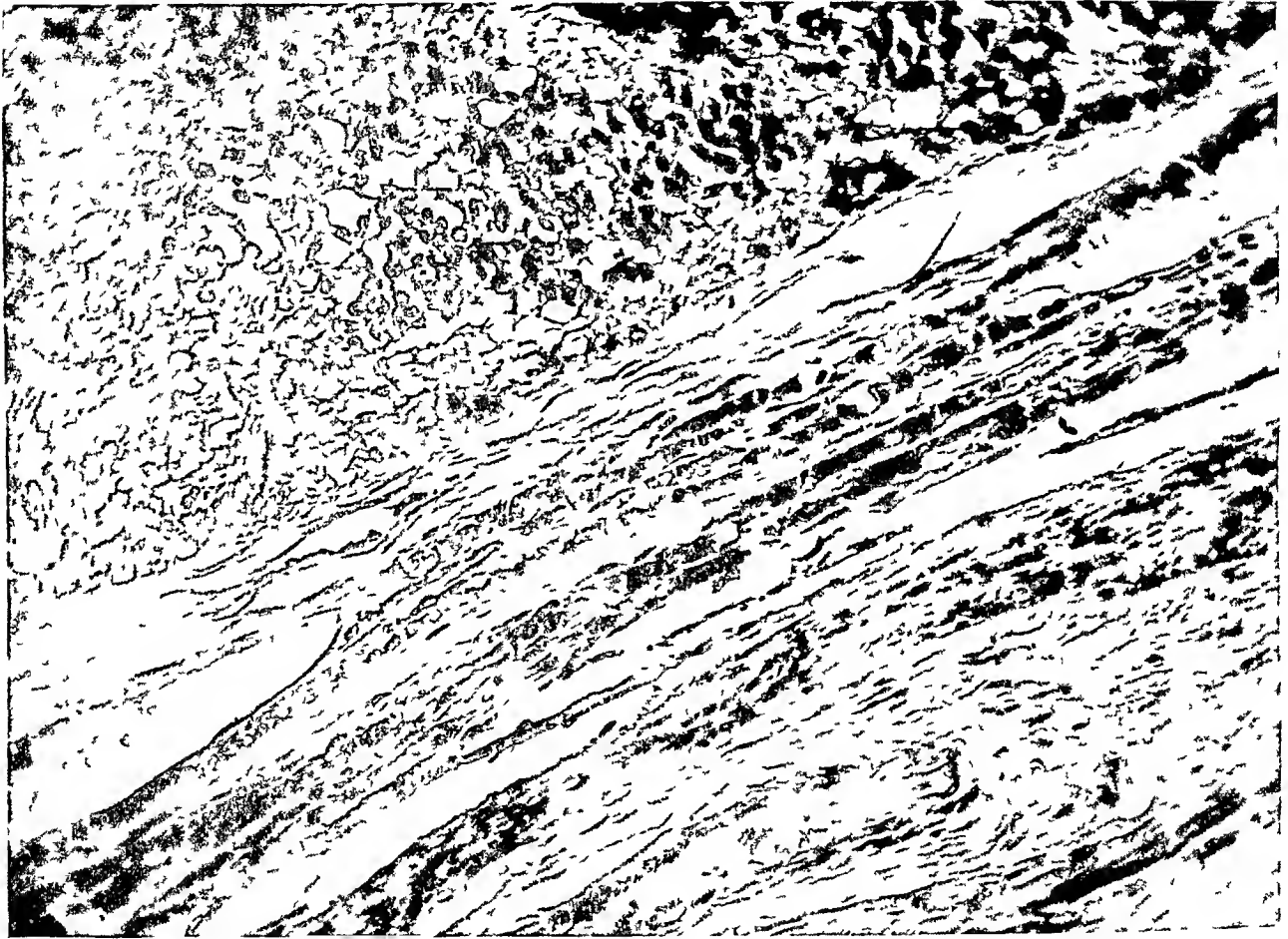


Fig 1—Compressed tissue of the anterior lobe, forming a thin, fibrotic capsule for the tumor. Litz obj, 8 mm apochromatic lens, periplanar 4.

nor the tuber cinereum were involved. The internal carotid arteries, especially the right, were somewhat compressed by the enlarged hypophysis, but could be easily separated from it.

A sagittal section through the hypophysis exposed a smooth, homogeneous, light grayish-brown surface with distinct blood vessels and several small, light orange-yellow patches. Underneath the capsule, also, there were several light gray, slightly transparent areas from 1 to 2 mm in diameter. The whole mass was soft and occupied almost the entire substance of the hypophysis, except for the thin capsule. The infundibulum appeared attached to the center of it.

The brain itself weighed 1,315 Gm. The leptomeninges at the base, especially about the oculomotor nerves, were slightly thickened with whitish lines. The leptomeninges over the convexity were smooth and transparent.

In addition, there were found parenchymatous degeneration of the myocardium, with dilatation of all the cardiac chambers, brown atrophy of the liver and passive congestion of the spleen.

Microscopic Examination—The posterior lobe of the hypophysis was well preserved and showed no marked deviation from its normal microscopic appear-



Fig. 2—Compressed zona intermedia of the anterior lobe, forming the posterior part of the capsule of the tumor. Leitz obj., 8 mm. apochromatic lens, periplanar 4.

ance. The anterior lobe was expanded to a thin shell which formed a capsule for the main mass of tissue occupying the gland (fig. 1). This capsule contained all the elements of the normal anterior lobe, but its cells were compressed and arranged in parallel cords separated by strands of fibrillar connective tissue. Small groups of basophil cells predominated, but there were also cords of principal cells and single eosinophil cells. Posteriorly, adjacent to the pars nervosa, this capsule contained all the remnants of the normal intermediate or boundary zone of the hypophysis. There were colloid-filled follicles lined by low cuboidal or flat epithelium and cords of principal cells, among which were scattered occa-

sional basophil cells. With all stains used, the colloid in these follicles was identical with that found in the main mass of the gland.

The main part of the hypophysis, the light gray-brown central mass, was composed of long and slender columnar cells, which were arranged radially about the blood vessels and connective tissue septums. On tangential sections, they appeared in palisade arrangement. Each cell had a delicate, finely granular cytoplasm and an oval nucleus occupying the central part of the cell. The chromatin formed fine granules and was evenly distributed within the nucleus. There were

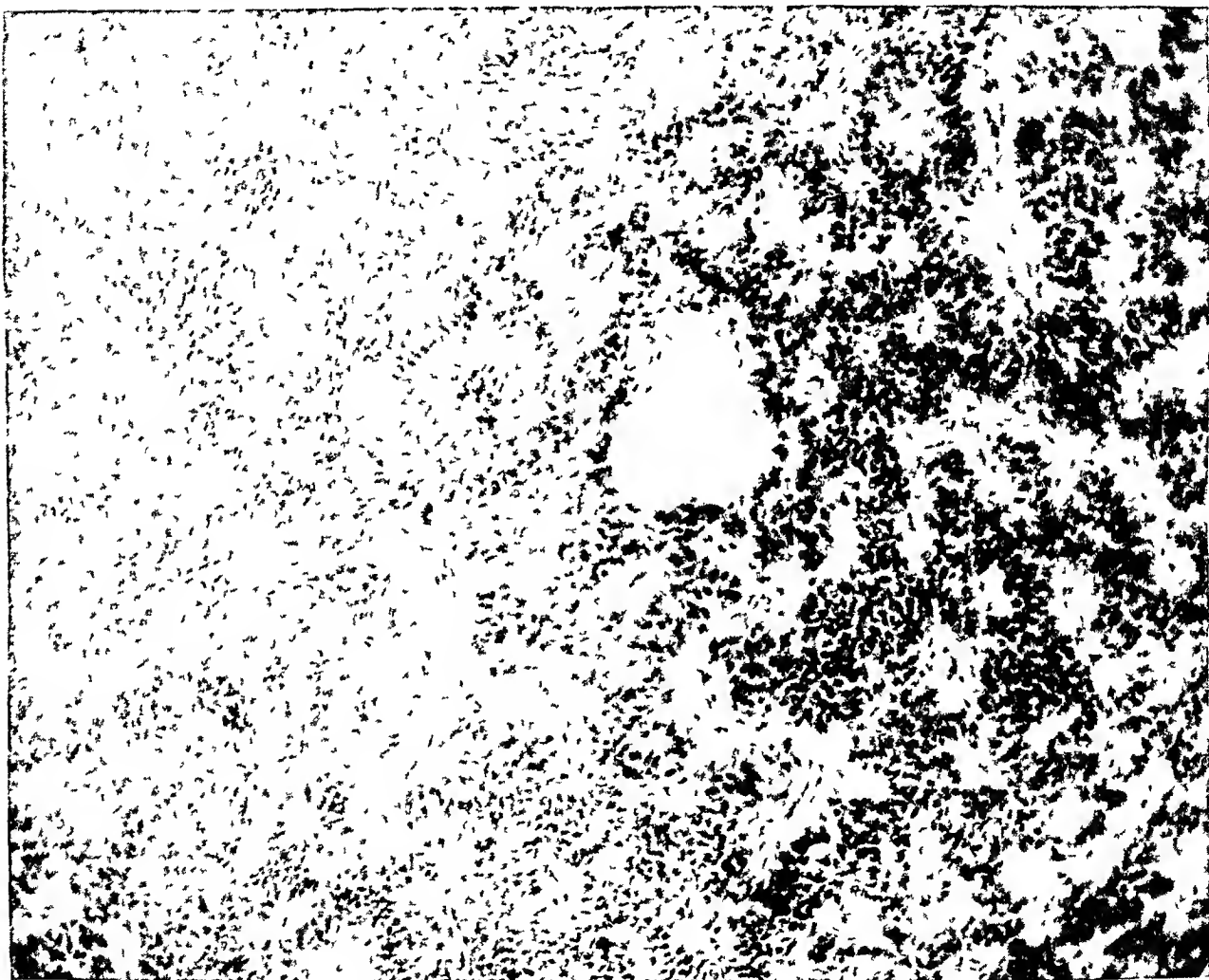


Fig 3—Low power view of fetal cell adenoma in the midportion of the anterior lobe, showing the characteristic palisade arrangement. Frozen section, Leitz obj, 8 mm apochromatic lens, periplanar 4.

fine lipid granules in the cytoplasm immediately about the nucleus. Wedged in between these cells, there were single small cells with deeply stained nuclei. There were also numerous large cells with an ample cytoplasm, which was filled by large fat droplets and by numerous hyaline droplets. The nuclei of these cells stained deeply and were often crenated.

Between the rings of columnar cells and the blood vessels were often spaces filled by a homogeneous, oxyphil, colloid-like material. This material at times was vacuolated. In it were suspended isolated nuclei resembling those of the

perivascular cells, as well as whole cells with vacuolated cytoplasm containing hyaline droplets. Throughout the tumor, but most numerous near the surface, were follicles and even small cysts up to 2 mm in diameter. They were filled by material similar to that described as occurring about the blood vessels and were lined by low cuboidal cells, so that they resembled the colloid-filled follicles of the thyroid gland.

With hematoxylin and eosin, this colloid stained pink, with Mallory's stain, either a deep blue or a light orange-yellow. With Kraus' polychrome methylene-

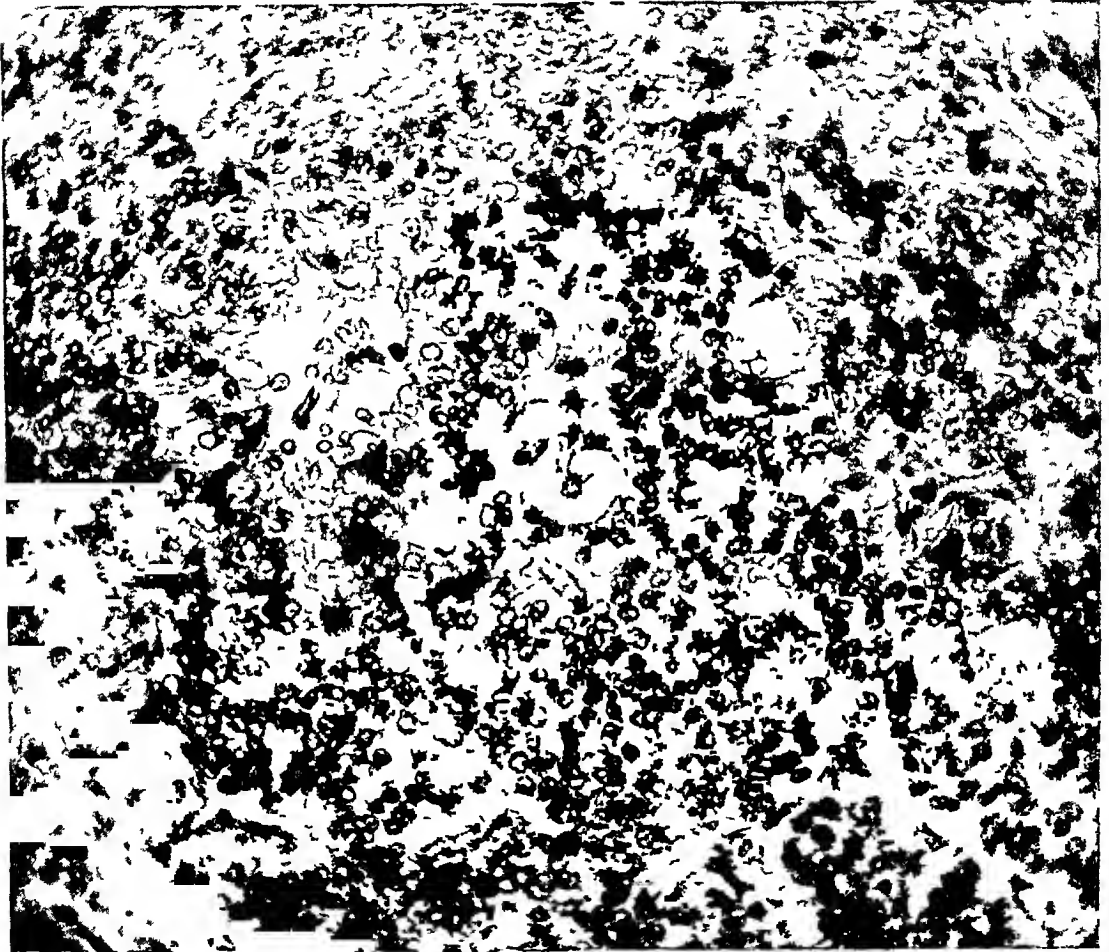


Fig 4—High power view of fetal cell adenoma in the midportion of the anterior lobe, showing the characteristic columnar cells, with intracellular and extracellular colloid droplets and the formation of colloid-filled spaces. Paraffin section, Litz obj, 4 mm apochromatic lens, periplanar 4.

blue-acid fuchsin-tannic acid stain,³ most of the colloid was light blue (fuchsinophobe). Fuchsinophil (red) and tannic acid-fast (violet) colloid were, however, also present. The origin of this colloid could readily be followed from droplets within the fetal cells. For, with each stain used, the same staining reaction was

3 Kraus, E. J. Das Kolloid der Schilddrüse und Hypophyse des Menschen, Virchows Arch f path Anat 218 107, 1914.

seen in the droplets within the fetal cells as was found in the adjacent colloid masses. Sometimes the entire cytoplasm of one or of several cells was transformed into the same homogeneous material. The colloid droplets could then be seen between the fetal cells and finally, in similar staining reaction, were gathered in the perivascular spaces and larger cysts.

With the sudan III stain, fine fat droplets were similarly seen in the cytoplasm of the cells, then between the cells and, finally, within the colloid-filled spaces. They appeared in these spaces in the form of free clusters and also within desquamated cells, but there were no "spheroids."

Anatomic Diagnosis—The anatomic diagnosis was fetal adenoma arising from the midportion of the anterior lobe of the hypophysis, healing chronic peptic ulcer of the stomach, with stenosis of the pylorus and marked gastric dilatation, calcium deposit in the renal tubular epithelium, and parenchymatous degeneration of the myocardium.

CASE 2—Clinical History—A colored woman, 36 years old, was admitted to the hospital in a semistuporous condition, from which she could not be roused. A history was obtained from relatives to the effect that for two years she had been suffering from frequent and severe headaches. She had taken to drinking large quantities of water. There was a consequent polyuria, especially nocturnally, but no loss of weight.

For the last five months, her vision had been failing progressively, and her headaches had begun to be more frequent and severe. In the last two weeks, she was oppressed with marked somnolence and slept almost constantly. Two days before admission, she became irrational and finally lapsed into deep stupor.

Physical Examination—The patient was rather well nourished and had a normal temperature and blood pressure, but a pulse rate of only 60. The pupils were irregular and dilated and did not react to light. The fundi were normal, except for a slight hyperemia of the disks. No papilledema was found. The results of physical and neurologic examination were otherwise negative.

One drop of urine reduced 5 cc of Hanes' solution. The urine was loaded also with albumin and contained a few hyaline casts. The blood chemistry showed a normal urea nitrogen. This excluded the possibility of uremic coma. The dextrose content of the blood returned a reading of 272 mg per hundred cubic centimeters. After one injection of 40 units of insulin, the blood sugar dropped to 70, and the glycosuria disappeared. Still the patient remained in coma, so that the diabetes could not have been its cause. A syphilitic basilar meningitis was also finally considered, but the Kahn reaction was negative. The patient died in less than twenty-four hours after entrance, before anything more could be done to clarify the diagnosis. Cerebrospinal fluid for a Wassermann reaction was not taken.

Postmortem Examination—Autopsy disclosed the essential pathologic changes in the brain. It weighed 1,000 Gm. Its convolutions were flattened. The right hemisphere was distinctly larger than the left, so that its transverse diameter was 8 cm, as compared with 6 cm for the left. The longitudinal diameter of both hemispheres was 17 cm. At the base of the brain, the space between the optic chiasma and the infundibulum was the site of a lobulated, cystic, light grayish-brown mass, 3 cm in diameter. It compressed the optic tracts, especially the left, the outlines of which were almost completely obscured. The right optic tract crossed the posterior third of the mass. Anteriorly and laterally, it was flanked by the anterior cerebral arteries. The anterior portion of the infun-

chibulum formed part of the mass and the stalk of the hypophysis originated from its inferior aspect

Coronal section through the mass revealed a cyst, 2.5 by 2.5 by 2 cm in diameter, occupying the right subthalamic region and extending into and replacing the infundibulum. Its center was to the right of the median line. It did not displace the hypophysis or its stalk. Dorsally and anteriorly, the cyst was bordered by the anterior commissure. It was filled by a thick, light yellowish-gray fluid. It was lined by a wall that averaged 2 mm in thickness. The wall was firm and dark reddish-brown, and contained several pinpoint-sized, hard, whitish deposits. The adjacent brain tissue was transformed into a soft, colloid-like substance.

The septum pellucidum was swollen and softened and contained numerous pinhead-sized, dark red patches. Similar areas were found in the lining of the



Fig 5—Low power view of a dermoid cyst of the right hypothalamus. Note the homogeneous content of the cyst, with fatty acid needles, the hornified pearls of squamous epithelium, the cartilage, the bone and the fetal hair structures (H), in the wall, with colloid degeneration and glia reaction in the adjacent brain tissue.

anterior horns of the lateral ventricles and in the anterior half of the corpus callosum. The lateral ventricles, especially the right, and the third ventricle were compressed, their lining was smooth.

As incidental observations, there were also chronic peptic ulcer of the stomach, bilateral salpingitis isthmica nodosa, syphilitic aortitis, brown atrophy of the heart and terminal bronchopneumonia.

Microscopic Examination—Tumor mass in region of infundibulum. About the cyst was a wall of dense fibrillar connective tissue which was loosely and, in circumscribed areas, densely infiltrated by lymphocytes. It also contained small deposits of hemosiderin. The inside of this wall was lined by several layers of squamous epithelium with a distinct basal layer of cuboidal cells. The inner-

most layer of squamous cells appeared loosened and in places was desquamated. The cyst was filled by a homogeneous substance with many fatty acid needles and remnants of degenerated squamous epithelial cells.

The wall contained also numerous whirls and clusters of hornified epithelial cells, in which keratohyaline granules could be demonstrated (method of Weigert). Foreign body giant cells were seen about the hornified masses. Here and there, one could find structures resembling fetal hair follicles.⁴



Fig 6—A fetal hair follicle in the wall of the cyst. Leitz obj., 8 mm apochromatic lens, periplanar 4.

There were also areas composed of numerous wide capillaries and scanty cellular stroma. Groups of coarse, irregular bone trabeculae with distinct osteoblasts were present. Adjacent to the bone there were small groups of lightly stained cuboidal cells with distinct membranes, uniformly vacuolated cytoplasm and round vesicular nuclei resembling embryonic fat cells.⁵

⁴ They were identical with the embryonic hair structures pictured by Fischel, A. *Entwicklung des Menschen*, Berlin, Julius Springer, 1929, p. 562.

⁵ Fischel (footnote 4, p. 559).

The fibrous tissue capsule about the cyst wall was surrounded in turn by a proliferation of fibrillar glia and microglia cells. At the base, the glia tissue was scanty, laterally and dorsally it was more abundant and passed into the brain tissue. In places, the glia tissue broke down into a homogeneous mass in which scanty and tortuous fibrils were distinguishable. About the cerebral vessels adjacent to the broken-down tissue there were "cuffs" of lymphocytes.

Sections from the parietal cortex showed the changes characteristic of dementia paralytica in the form of perivascular round cell infiltrations of the leptomeninges

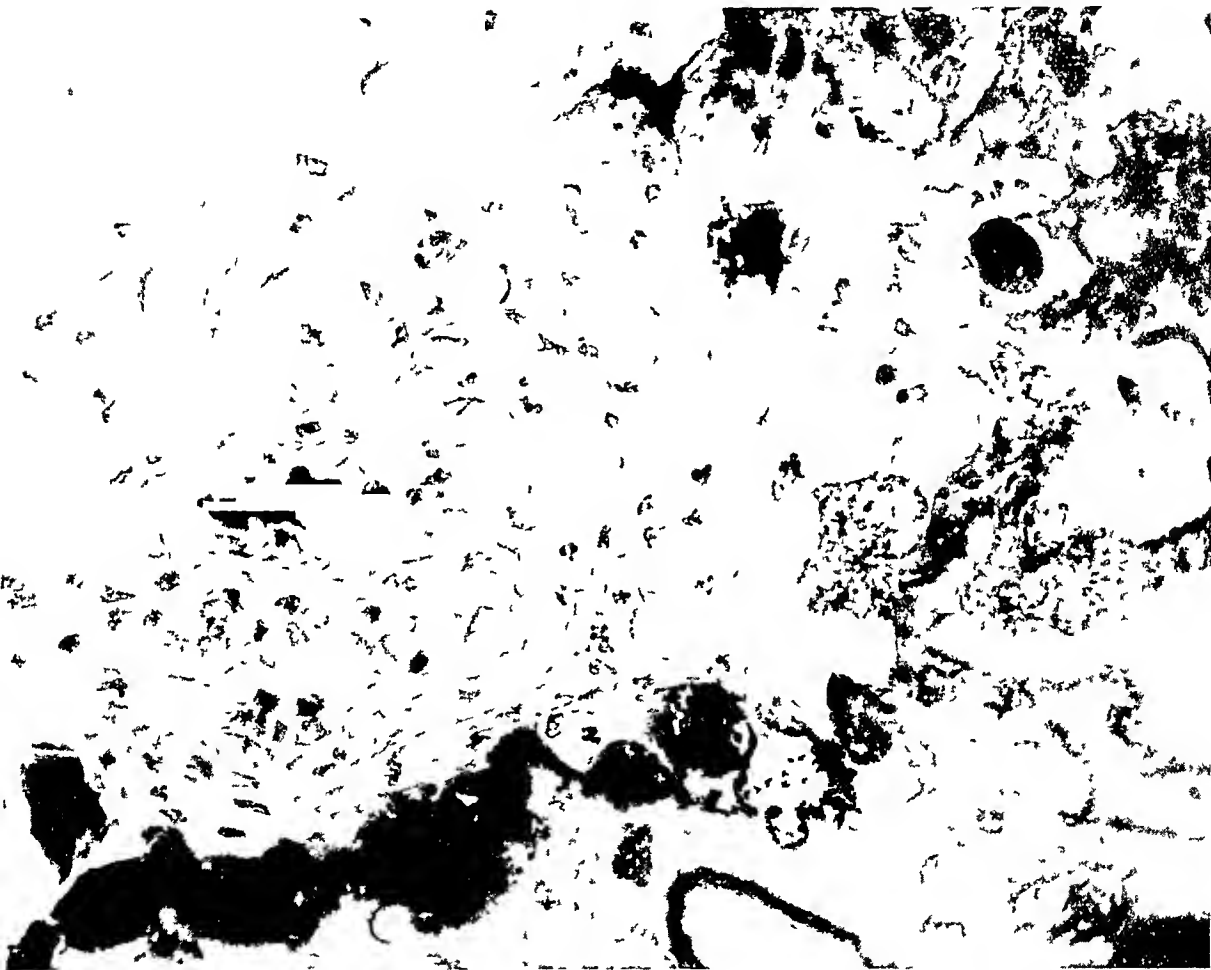


Fig 7—A group of embryonic fat cells in the wall of the cyst. Note the vesicular nuclei and the regular vacuolation of the cytoplasm. Leitz obj, 4 mm apochromatic lens, periplanar 4.

and the cortex, with degeneration and rarefaction of the ganglion cells and adventitial iron deposition.

The hypophysis was slightly excavated by the tumor mass. Its structure was well preserved, however, except for an increase of the interstitial tissue, which in places formed islands up to 1 mm in diameter. Among the cells of the anterior lobe, the basophil elements predominated. The posterior lobe was apparently unchanged.

Anatomic Diagnosis—The anatomic diagnosis was dermoid cyst of the brain occupying the right hypothalamic region and the infundibulum, colloid degeneration of the adjacent brain tissue, hemorrhages and softening of the septum pellucidum and the anterior half of the corpus callosum, complete atrophy of the left, and partial atrophy of the right, optic tract, syphilitic aortitis, terminal bronchopneumonia, and paretic meningo-encephalitis

COMMENT

The tumor described in the first case was probably an incidental observation. The entire clinical picture could be well accounted for on the basis of the peptic ulcer with pyloric stenosis, gastric dilatation and alkalosis. The tumor may have been a factor in the patient's death, but the brief clinical study precludes any definite statement to this effect.

It was apparently an adenoma of the hypophysis. It was not a simple hyperplasia, because it was definitely encapsulated. It was not a carcinoma, because it showed a definite alveolar arrangement, with no anaplasia, no infiltration, no erosion of the sella and no metastases.

It was an adenoma, but of rather an odd type. Its cells did not recall any of the chromophobe or chromophil elements of the pars anterior of the adult gland. Neither did they look like transitional cells or pregnancy cells. The high columnar cells in palisade arrangement, were strikingly different from any of these cell types. They did, however, resemble another type, namely, the indifferent cell of the fetal hypophysis. The whole adenoma tissue recalled the pars glandularis of a fetal hypophysis.

In 16 mm embryos, the simple hypophyseal sac pinched off from its connection with the craniopharyngeal duct is lined uniformly by a simple layer of high cylindric epithelium. The posterior wall in contact with the pars nervosa is relatively stationary in growth. In the anterior wall there is a rapid proliferation to form a mass of columnar cells, this mass bulges forward and then curls laterally to enclose the pars posterior with an incomplete ring of glandular tissue. The pars anterior of the hypophysis in the third month of fetal life is composed almost entirely of these same high cylindric cells, arranged radially about the blood vessels and connective tissue septums like palisades (Kraus²). These cells, like those found in the adenoma, have a delicate, finely granular cytoplasm, and oval centrally placed nuclei with a finely granular evenly distributed chromatin.

Rapidly, these undifferentiated fetal cells begin to mature. From them the entire structure of the adenohypophysis differentiates. Eosinophil cells are first developed. Then basophil cells appear and finally principal cells. The undifferentiated cells are in part slowly replaced

by differentiated ones, and the rest are further submerged by the rapid proliferation of the more mature elements. By the fifth month, they are reduced to a small proportion of the gland. At birth, relatively few are present. But even then, and at all ages throughout life, small groups of these undifferentiated columnar cells may be seen scattered among the differentiated elements (Cooper⁶). They are found in the lining of the vesicles in the intermediate zone and as isolated groups throughout the substance of the anterior lobe especially in its lateral parts.

It is generally conceived that the differentiated cells can perpetuate themselves in cycles with reversible transitions from one type to another. But these fetal cells are a constant source for new series of differentiations into principal cells, eosinophil cells, basophil cells, etc. Until at least early middle age, new series are being constantly started from them (Loewenstein⁷). These embryonal cell rests, in keeping with Cohnheim's theory, may thus be the indirect origin of adenomas of any differentiated cell type, which mature as they grow, or may directly originate an adenoma of undifferentiated fetal cell type.

The number of reported cases of fetal cell adenoma is small. As scanty as are fetal cells among the mature elements of the adult hypophysis, so infrequent are the fetal cell adenomas in comparison with the mature cell adenomas of the hypophysis. Loewenstein described a case of alveolar fetal cell adenoma. Kraus¹ presented a study of twenty-five cases of adenoma of the hypophysis. They included every possible variety and combination of hypophyseal adenoma together with two cases of fetal cell tumor. One was a malignant fetal cell adenoma, and in the same gland an area of chief cell hyperplasia, as well as another area of simple fetal cell hyperplasia were also found. The other was an adenoma-like fetal cell hyperplasia. These tumors usually begin after the age of thirty, when the differentiation of fetal cells into mature cells stops. Kraus was able to find transitions from fetal cells to principal cells in his cases. None was found in my case of fetal cell adenoma. All the cells were of the long, columnar undifferentiated, fetal type.

They were arranged in columns and in palisades about the blood vessels. Often between them and the vessels were colloid-filled spaces. Colloid-filled follicles and even small cysts were formed, especially just beneath the capsule. The colloid was a prominent feature of the

6 Cooper, E. *Histology of Human Endocrine Organs at Various Ages*, New York, Oxford University Press, 1925.

7 Loewenstein, C. *Die Entwicklung der Hypophyse Adenome*, *Virchows Arch f path Anat* **188** 44 1907.

microscopic sections The cysts could even be seen by the naked eye, just as they may often be seen in the intermediate zone of the normal hypophysis bordering the posterior lobe There are three possibilities for the origin of hypophyseal colloid It may be a product of active secretion by differentiated cells of various kinds Some hold that there is a different secretion from each type of cell, and there is good clinical evidence to support this view Others hold that all the mature cell types are but successive stages in a single secretory process The colloid may also be the product of degeneration of differentiated or of undifferentiated cells Finally, it may appear as a vestige of the old external secretion, a fruitless secretion, within the pinched-off daughter cysts of Rathke's pouch⁸ In the adult gland, all three possibilities may be realized, but how to distinguish the three types of colloid is a difficult matter

Only part of the colloid-filled follicles were lined by the cells of Rathke's pouch The rest were lined wholly or in part by differentiated cells of all kinds, with only an occasional undifferentiated cell One could trace the origin of each type of colloid from the substance of the adjacent cells, but here differentiation ended Iodine was never found in appreciable amounts in any of these three types of colloid, except when therapeutically administered, so that there were no means of chemical identification⁹ Beyond reasonable doubt, the anterior lobe of the hypophysis has an internal secretion, but it is probably not stored to any great extent within the colloid masses Most of the secretory colloid is probably unloaded directly into the blood stream (Maurer,¹⁰ Rasmussen¹¹) Kraus concluded that most of the colloid as it is found in the adult gland is not the product of an active secretion, like that of the thyroid gland, and not a stored vestige of the old external secretion, but is a product of cellular degeneration

Morphologic evidence is not enough to establish definitely physiologic qualities, but it, at least, indicated that the colloid seen in the fetal adenoma arose also, most probably, by cellular degeneration The perivascular colloid accumulations had no resemblance to the vesicles of

8 Erdheim, J Ueber Hypophysentumoren, *Wien med Wchnschr* **74** 425, 1924

9 Wells, H G Chemical Pathology, Philadelphia, W B Saunders Company, 1925

10 Maurer, C, and Lewis, D The Structure and Differentiation of the Specific Cellular Elements of Pars Intermedia of the Hypophysis of the Domestic Pig, *J Exper Med* **36** 141, 1922

11 Rasmussen, A T Histological Evidences of Colloid Absorption Directly by Blood Vessels of the Human Hypophysis, *Quart J Exper Physiol* **17** 149, 1927

Rathke's pouch It was not readily conceivable that the undifferentiated fetal cells would be elaborating, as yet, any active secretion Cells in the course of degeneration could be seen among the intact ones, and desquamated degenerated cells were found suspended within the colloid The observations in the fat stains also bespoke a degenerative origin for this colloid, because "spheroids" such as those seen in the thyroid gland as marks of its secretory activity were altogether absent (Jaffé,¹² Kraus¹³)

In the normal gland, this formation of colloid is most active in the posterior part of the anterior lobe, adjacent to the pars nervosa Here are also found the vesicles derived from Rathke's pouch Numerous colloid cysts and follicles therefore characterize this intermediate or boundary zone ("Markschicht"), or cyst zone, of the anterior lobe They distinguish it from the posterior lobe behind, and the rest of the anterior lobe in front This and its position have caused a frequent confusion of the intermediate zone of man with the colloid-bearing pars intermedia seen in lower animals

In animals such as the pig, calf, cat, rat, dog, frog, woodchuck, opossum, etc., the hypophysis presents a well developed pars intermedia with characteristic histologic structure and presumably a specific function¹⁴ It lies between the hypophyseal cleft and the pars posterior It is derived by a special line of differentiation from the columnar cells of the posterior walls of Rathke's pouch, just as the pars anterior is derived by another line of differentiation from the anterior wall¹⁵ It is composed of some small, undifferentiated cells but mostly of large, highly differentiated, oval or polyhedral cells with a finely granular basophil cytoplasm and single or multiple nuclei These cells have no counterpart in the pars anterior They are arranged in trabeculae and in palisades about the blood vessels They form perivascular spaces and larger follicles filled by a colloid that in origin is partly degenerative and partly secretory This pars intermedia presents all extremes of variation In one species it may be a prominent part of the gland and in another species insignificant In different members of a given species it varies widely, and even in the same individual it changes from time to time (Rasmussen¹⁴)

12 Jaffé, R. H. Histologic Studies on the Fat Content of the Normal Human Thyroid, *Arch. Path.* **3** 955, 1927

13 Kraus, E. J. Die Lipoidsubstanzen der menschlichen Hypophyse und ihre Beziehung zur Sekretion, *Beitr. z. path. Anat. u. z. allg. Path.* **54** 520, 1912

14 Rasmussen, A. T. Morphology of Pars Intermedia of the Human Hypophysis, *Endocrinology* **12** 129, 1928

15 Thaon, P. *L'hypophyse*, Paris, G. Doin, 1907

In man, the pars intermedia, if present at all, is a rudimentary structure Erdheim,¹⁶ Berblinger,¹⁷ Dayton,¹⁸ Kasche, Benda and others insisted that man has no pars intermedia Stendell,¹⁹ Biedl,²⁰ Marburg,²¹ Aschoff -- and Schoenig²² could not reconcile themselves to the view that in man the pars intermedia should be abruptly dropped They have made a searching study for homologues in man of the pars intermedia of animals One after another, various structures noted in the human hypophysis have been labelled in homology, "pars intermedia"

The zona intermedia, as seen in man, has nothing to do with a pars intermedia Its cells are identical in origin, structure, function and variation with those of the rest of the anterior lobe It is simply part of the pars anterior which differs from the rest only in its greater content of colloid Other structures have been even more readily confused The posterior wall of Rathke's pouch, in man as well as in lower animals, is a multipotent layer Besides differentiating into the cells of the pars intermedia as it does to such an extent in lower animals, it can differentiate into a great variety of other structures Its pharyngeal origin accounts for the appearance of ciliated and goblet cells, squamous cells and glandlike structures resembling mucous or salivary glands Basophil cells and principal cells with colloid follicles like those of the anterior lobe are also formed from it, and undifferentiated fetal cells are found scattered among them Whatever it differentiates, the posterior wall pushes into the adjacent pars nervosa in the same position that is occupied by the true pars intermedia Basophil cells of the pars anterior proper, which have originated from the anterior wall of Rathke's pouch, also wander into the posterior lobe

But all these do not constitute a pars intermedia, even if they lie in the same position They have no resemblance to pars intermedia

16 Erdheim, J Pathologie der Hypophysen-Geschwulste, *Ergebn d allg Path u path Anat* **21** 482, 1926

17 Berblinger, W Kritisches zur Hypophysen-Pathologie, Frankfurt *Ztschr f Path* **35** 497, 1927

18 Dayton, T R Ueber die sogenannte Pars intermedia der menschlichen Hypophyse, *Ztschr f Anat u Entwicklungsgesch* **81** 359, 1926

19 Stendell, V Die Hypophysis cerebri, Lehrbuch der vergleichenden mikroskopischen Anatomie, Jena, Gustav Fischer, 1914

20 Biedl, A Die funktionelle Bedeutung der einzelnen Hypophysenanteile, *Endokrinologie* **3** 241, 1929, *Internal Secretory Organs*, New York, William Wood & Company, 1913

21 Marburg, O Zur Frage der Pars intermedia der menschlichen Hypophyse, *Endokrinologie* **5** 198, 1929

22 Aschoff, L Gibt es eine Pars intermedia in der menschlichen Hypophyse? *Beitr z path Anat u z allg Path* **84** 273, 1930

23 Schoenig, A Die extra-uterinen Entwicklungsphasen der Pars intermedia der menschlichen Hypophyse, Frankfurt *Ztschr f Path* **34** 482, 1926

cells They have the same structure as the pars anterior elements They undergo the same changes as do the pars anterior cells in pregnancy, castration and many pathologic conditions They are still to be identified with the pars anterior and not with the pars intermedia The pars intermedia is simply one of the highly specialized differentiations which the posterior wall of Rathke's pouch can originate, and it has no homologue in these other structures described as occurring in man

There are some indications, however, that man really has a pars intermedia, rudimentary and insignificant and functionless though it is Maurel,¹⁰ Lewis,²⁴ Lewis and Lee,²⁵ Maibug,²¹ Loeffler²⁶ and others have described from time to time the occasional finding in the posterior lobe of groups of cells that resemble somewhat those of the pars intermedia I found similar cells incidentally in a case a report of which I recently submitted for publication It is almost impossible, however, to establish the identity of these small and infrequent cellular structures because of the poor fixation of most human material In two cases in which autopsy was performed soon after death, Dr Bensley showed me cells in the pars posterior of the hypophysis that greatly resembled those of the pars intermedia of lower animals But no absolutely specific histologic identification of them has as yet been made

As one argument against its presence in man, Berblinger²⁷ pointed out that no tumor of the pars intermedia had ever been definitely established Ewing,²⁸ however, quoted reports on three cases by Boyce and Beadles and Cushing, in which the relations of the hypophyseal tumor suggested an origin from the pars intermedia Lewis²⁴ offered another case The tumors were composed of cords of large cells, lying in acinar arrangement about colloid-filled spaces They thus resembled thyroid gland tissue somewhat as does the pars intermedia Two of these tumors were attached to the pedicle of the hypophysis above the sella apparently originating from the pars tuberalis The other two were adenomatous tumors that originated outside the main substance of the pars anterior and compressed it The resemblance of these tumors to

24 Lewis, Dean A Contribution to the Subject of Tumors of the Hypophysis, *J A M A* **55** 1007, 1910

25 Lewis, Dean, and Lee, F C On the Glandular Elements in the Posterior Lobe of the Human Hypophysis, *Bull Johns Hopkins Hosp* **41** 241, 1927

26 Loeffler, E Ueber ortsfremde Zellen und Geschwulste im Hinterlappen und im Stiel der Hypophyse, *Virchows Arch f path Anat* **274** 326, 1929

27 Berblinger, W Die genitale Dystrophie in ihrer Beziehung zu Störungen der Hypophysenfunktion, *Virchows Arch f path Anat* **228** 151, 1920

28 Ewing, J Neoplastic Diseases, Philadelphia W B Saunders Company, 1928

the pars intermedia of animals is rather vague and is based only on the presence of numerous colloid-filled cysts. Nor does their origin outside the main mass of the pars anterior establish them as tumors of the pars intermedia, for nests of pars anterior cells are scattered all along the stalk and may just as well have produced adenomas which by colloid degeneration came to resemble somewhat, pars intermedia tissue.

The colloid masses and follicles of the adenoma herein reported also resembled these tumors. The columns and palisades of large, undifferentiated cells conformed to none of the more usual adenomas of the anterior lobe. The main substance of the anterior lobe itself was seen to form a thin capsule around the tumor mass. It was suggested that here at last one was dealing with the much sought for tumor of the pars intermedia. But this, too, was no tumor of the pars intermedia. It was composed of undifferentiated fetal cells and not of differentiated pars intermedia cells. Its abundant colloid, like that of the intermediate zone of the normal hypophysis, was a degenerative product from the undifferentiated cells rather than a secretory one. The tumor did not compress the anterior lobe, but rather expanded the lobe into a thin shell, which completely encapsulated it. Apparently it had started in the midportion of the pars anterior, for the compressed anterior substance surrounded it on all sides, separating it from the sella, the operculum and the infundibulum. Even posteriorly, the compressed old zone intermedia, with its flattened cysts, separated it from the pars nervosa and denied it any possible origin from a pars intermedia. It was finally classified, therefore, as a fetal cell adenoma arising from the midportion of the pars anterior of the hypophysis.

The second case was that of a dermoid cyst of the hypophyseal area. Tissues adjacent to the hypophysis have a special predilection for inclusion tumors of all kinds. Many of these tumors present cysts and nodules filled by cholesteatomatous material that resembled mother-of-pearl, and so have been given the name of "Perilegeschwulste." In 1897, Bostroem²⁹ analyzed these tumors and pointed out that the intracranial cholesteatomatous cysts arise by embryonal inclusion of ectodermal cells, which are carried into the brain vesicles during the closure of the neural canal. Cysts with but few squamous epithelium cells and much cholesteatomatous material he classed as "simple cholesteatomas." If the squamous epithelial cell masses were more abundant, he called them "epidermoids," to emphasize their origin from epidermis. If other special structures of the skin were included, such as fetal hairs, sweat glands and sebaceous glands, he classed them as "dermoids," since

²⁹ Bostroem, E. Ueber piale Epidermoide, Dermoide und Lipome, und durale Dermoide, *Centralblatt f. allg. Path. u. path. Anat.* 8 1, 1897.

they were derived from the whole dermis. These unigerminal tumors pass by the addition of mesodermal and endodermal elements gradually into the field of the bigerminal teratoid tumors and finally into the trigerminal true teratomas. One step further carries them to the fetal implantations or inclusions foetus in foetu, the double monsters.

Then Eidheim¹⁶ traced a well defined group of tumors of this region to included remnants of the cranopharyngeal pouch. He found nests of pharyngeal epithelium in ten of thirteen cases which he examined carefully for them. They were all in the midline, but were scattered from the base of the brain all the way along the course of the hypophyseal duct to the nasopharynx. The inclusion tumors of the hypophyseal duct arise from these nests, at any point along its course. They appear in the hypophysis itself as well as in tissue adjacent to it, but adhere to the midline.

They, too, in complexity of structure present a progressive series. There are simple cysts arising by distention of Rathke's pouch. They are sometimes lined in part by a ciliated epithelium, which indicates their origin from the nasopharynx and distinguishes them from ependymal, adenomatous or ectodermal inclusion cysts. The "epidermoid" tumors from the hypophyseal duct include intracystic papillomas, adamantinoid tumors and benign and malignant squamous cell tumors of all kinds. Often they are prone to hemorrhages and degenerative changes which lead to the metaplastic production of cartilage, bone and even bone-marrow. Hemosiderin deposited from the hemorrhages may be confused with melanin. Pseudoxanthomatous, fat-laden cells may be taken for notochord tissue. Glia cells of the adjacent brain tissue may be taken for part of the tumor, and so these degenerating hypophyseal duct tumors be mistaken for teratomas.

Eidheim sharply distinguished these tumors from the dermoid tumors of Bostroem. Hypophyseal duct tumors adhere to the midline, the dermoid tumors do not. He found keratohyaline granules in the latter, but not in the former. Subsequent study failed to confirm this distinction, because when fresh material was used, keratohyaline granules were found just as readily in tumors of the hypophyseal duct as in the others.³⁰ Fetal hair follicles and sebaceous glands, or endodermal elements, were still considered as irrefutable marks of dermoid origin, as opposed to hypophyseal duct origin. But, according to Ewing, it is even possible for true teratoid tumors to arise, autochthonously by metaplasia from hypophyseal duct remnants. Practically all absolute

30 Horrax, G. A Consideration of Dermal Versus Epidermal Cholesteatomas Having Their Attachment in Cerebral Envelopes, *Arch. Neurol. & Psychiat.* 8: 265, 1922.

distinction therefore vanishes, except that the latter tumors adhere to the midline. Both groups, indeed, are derivatives of embryonically included stratified squamous epithelium. Bostroem's tumors are derived from external ectoderm and Erdheim's tumors from oral ectoderm. The tumor of the second case was definitely of squamous epithelial character. The central cyst was filled by cholesteatomatous material. Its wall was lined by stratified squamous epithelium with intercellular bridges, keratohyaline granules and hornified epithelial pearls. There were calcium deposits and degenerative and reactive changes in the adjacent brain tissue. The cartilage and bone and vascular stroma of the cyst wall might be taken as metaplastic in origin, but the fetal hair follicles take it undeniably from the class of epidermoids to that of dermoids. The cells resembling embryonic fat cells are further evidence of this. These structures and the asymmetric position of the tumor place it with the dermoid cysts of external ectodermal inclusion, rather than with the hypophyseal duct tumors of oral ectodermal inclusion.

Since Erdheim's clarification of the subject, a considerable number of hypophyseal duct tumors have been described (Duffy,³¹ Jackson,³² Kanavel³³). Of external ectoderm inclusion tumors many of the simple cholesteatomas and epidermoids not containing hair, have also been described (Bailey,³⁴ Schuster³⁵). Hair-containing cholesteatomas, or true dermoid cysts, are less numerous (Teutschlander,³⁶ Rand,³⁷ Tannenham³⁸ Koprewa³⁹). Globus⁴⁰ described a case almost identical with the one here reported except that sebaceous gland cells were present. He distinguished these from embryonic fat cells because their nuclei were pyknotic and their cytoplasmic vacuoles irregular.

31 Duffy, W. C. Hypophyseal Duct Tumors, *Ann Surg* **72** 537, 1920

32 Jackson, H. Craniopharyngeal Duct Tumors, *J A M A* **66** 1082, 1916

33 Kanavel, A. B., and Jackson, H. Cysts of the Hypophysis, *Surg Gynec Obst* **26** 61, 1918

34 Bailey, P. Cruveilhier's "Tumeurs Perlees," *Surg Gynec Obst* **31** 390, 1920

35 Schuster, J. Dermoid Cyst of Right Frontal Lobe, *Schweiz Arch f Neurol u Psychiat* **16** 327, 1925

36 Teutschlander, O. R. Zwei seltenere tumorartige Bildungen der Gehirnbasis, *Virchows Arch f path Anat* **218** 224, 1914

37 Rand, C. W. Intracranial Dermoid Cyst, *Arch Neurol & Psychiat* **14** 346, 1925

38 Tannenham, C. Dermoid Cyste des dritten Gehirnvatrikels, *Wien klin Wchenschr* **10** 494, 1897

39 Koprewa, G. Eine Dermoidcyste in der linken Grosshirnhemisphaere, *Med Klin* **23** 645, 1927

40 Globus, J. H. Teratoid Cyst of the Hypophysis, *Arch Neurol & Psychiat* **9** 417, 1923

More complex, bigeminal teratoid tumors are infrequent (Derman⁴¹) Gautier⁴² collected from the literature only twenty-five cases described with sufficient histologic accuracy to warrant their classification with teratoid tumors. True tergeminal teratomas are rare indeed. Sztanojevits⁴³ described one case and Saxer⁴⁴ another. Kraus⁴⁵ recently completed the series by reporting an epignathous monster of the hypophyseal region.

Tumors of the hypophysis and tissues adjacent to it have attracted particular attention because of the special syndromes with which they are associated. The hypophysis itself has several distinct endocrine functions which may be either stimulated or destroyed. The hypophyseal region about it is an apex of vegetative control. When one attempts to analyze the syndromes produced by these tumors, one wanders into uncertain territory. Hypophyseal tumors may be eliciting symptoms by secondary pressure on the midbrain. Tumors of the midbrain may manifest themselves only through destruction or dysfunction of the hypophysis.⁴⁶

Tumors that involve one part while leaving the other perfectly free are, however, equivalent in man to experimental selective extirpation in animals. They contribute to the evidence by which one may some day be able properly to assign the various functions of this region. Such cases have already taught that many of the functions that formerly were regarded as belonging to the hypophysis are really functions of the midbrain (Illig⁴⁷).

For a long time, the posterior lobe of the hypophysis was implicated in the cause of diabetes insipidus, because lesions of the hypophysis were often associated with this syndrome. In the early experiments on

41 Derman, G. L. Zur Kenntnis der Teratome des Gehirns, *Virchows Arch f. path. Anat.* **259** 767, 1926.

42 Gautier, R. Zur Kenntnis der Mischgeschwulste der Hypophysengegend, *Frankfurt Ztschr. f. Path.* **19** 247, 1916.

43 Sztanojevits, L. Mannfaustgrosses, lange Zeit hindurch ohne objective Symptome bestehendes und plötzlich zum Tode führendes Klein-Hirnteratom, *Neurol. Centralbl.* **37** 784, 1918.

44 Saxer, F. Ein zum grössten Theil aus Derivaten der Medullarplatte bestehendes grosses Teratom im dritten Ventrikel eines sieben wöchentlichen Kindes, *Beitr. f. path. Anat. u. z. allg. Path.* **20** 399, 1897.

45 Kraus, E. J. Ueber ein epignathisches Teratom des Hypophysengegend, *Virchows Arch. f. path. Anat.* **271** 546, 1929.

46 Lereboullet, P., Mouzon, J., and Catholu, J. Infantilisme dit hypophysaire par tumeur du troisième ventricule, intégrité de l'hypophyse, *Rev. neurol.* **28** 154, 1921.

47 Illig, W. Geschwulste der Hypophyse beziehungsweise der Hypophysengegend und Zwischenhirn, *Virchows Arch. f. path. Anat.* **270** 549, 1928.

animals, destruction of the pars posterior resulted in polyuria, which injections of extracts from the posterior lobe relieved. However, it was then observed that pathologic processes involving practically the whole hypophysis were not necessarily followed by diabetes insipidus. Traumatic, infectious and neoplastic processes of all kinds affecting the region of the tuber cinereum and leaving the hypophysis anatomically intact could alone produce diabetes insipidus (Leschke,⁴⁸ Bosco⁴⁹)

In reevaluating the results of hypophysectomy it was noted that polyuria did not occur in every case. When polyuria occurred following hypophysectomy, pathologic changes, such as necrosis, cysts, hemorrhages, tigriolysis, etc., were always found also in the tuber cinereum. When polyuria did not occur, these changes were absent (Karlik⁵⁰)

On repetition of the experiments, extirpation of as much of the hypophysis as possible (fully 95 per cent or more) did not lead to polyuria if the base of the brain was avoided (Bailey and Bremer,⁵¹ Fulton and Bailey⁵²). Superficial lesions of the tuber cinereum produced polyuria even when the hypophysis was intact.

Clearly this indicated that diabetes insipidus is not a symptom of depletion (an "Ausfallscheinung") of the pars posterior, but is a result of specific damage to the tuber cinereum at the base of the brain. The two cases herein reported, despite the brief clinical observation of them, lend some support to this view. In the first, the fetal cell adenoma had crushed the original hypophysis into a thin shell around it, yet there was apparently no polyuria. In the second, the clinical picture was complicated by the parietic changes, but the dermoid cyst had produced extensive damage in the hypothalamus and had affected the hypophysis but little, and there was polyuria. In Globus's case, too, there was diabetes insipidus with the hypophysis intact.

The hypophysis has been given a rôle also in sugar metabolism. Glycosuria and diabetes are often associated with acromegalic tumors. Injury to the hypophysis causes a transient hyperglycemia. In the case of the dermoid cyst here reported, the hypophysis was intact, yet there were hyperglycemia and glycosuria which yielded promptly to insulin and caused confusion with diabetes mellitus. In fact, the same hyper-

48 Leschke, E. Beitrage zur klinischen Pathologie des Zwischenhirns, *Ztschr f klin Med* **87** 201, 1919

49 Bosco, G. La patogenia de la diabetes insipida, *Semana med* **2** 477, 1925

50 Karlik, L. N. Zur Frage der sogenannten hypophysaeren Polyurie, *Ztschr f d ges exper Med* **61** 5, 1928

51 Bailey, P., and Bremer, F. Experimental Diabetes Insipidus, *Arch Int Med* **28** 773, 1921

52 Fulton, J. F. and Bailey, P. Brain Tumor in Region of Third Ventricle, *J Nerv & Ment Dis* **69** 1, 145 and 261, 1929

glycemia and glycosuria seen with tumors of the hypophysis may be seen with tumors of the hypothalamus that do not involve the hypophysis⁵³ Injury of the tuber cinereum gives an even greater hyperglycemia than does that of the hypophysis Therefore, a "sugar center" has been postulated in the tuber cinereum, rather than in the pituitary body

There is no definite "sugar center" in the hypophysis Neither is there one in the tuber cinereum or in any other part of the brain Tumors in other parts of the brain may occasionally cause glycosuria Injury of any part of the brain can cause hyperglycemia and glycosuria (Hiller⁵⁴) While the hypothalamic diabetes cannot be ascribed to any definite "sugar center" in this region, it is known that the diencephalon has a certain regulatory influence on various vegetative functions, including the metabolism of fat, salt, water and sugar, and sleep (Fulton and Bailey⁵²) It is damage to this region that is chiefly responsible for the adiposity, the diabetes mellitus and the diabetes insipidus formerly ascribed to hypophyseal lesions

SUMMARY AND CONCLUSIONS

A fetal cell adenoma of the hypophysis and a dermoid cyst of the hypothalamus are reported The first tumor resembled one of the so-called "pars intermedia tumors" It originated, however, not from a pars intermedia, but from the midportion of the pars anterior It was composed not of the specific differentiated pars intermedia cells, but of undifferentiated fetal cells If man has a pars intermedia comparable with that of lower animals, it is rudimentary, variable and functionless There is, as yet, no histologic proof establishing its presence

The dermoid cyst belonged to the group of inclusion tumors of the hypophyseal area It was derived from embryonal rests of cranial external ectoderm included during the invagination of the brain vesicles It was related to Erdheim's tumors derived from rests of oral ectoderm invaginated with Rathke's hypophyseal pouch It involved the hypothalamus, leaving the hypophysis relatively intact, and yet produced the diabetes insipidus and the diabetes mellitus usually ascribed to hypophyseal lesions The diencephalon rather than the hypophysis is chiefly responsible for these syndromes

53 Klug, W Die Hypophyse und der Zuckeraushalt des Koerpers, Deutsche Ztschr f Chir **212** 5, 1928

54 Hiller, F, and Grinker, R The Nervous Regulation of Sugar Metabolism, Arch Neurol & Psychiat **22** 919, 1929 Hiller, F, and Tannenbaum, A The Nervous Regulation of Sugar Metabolism, Arch Neurol & Psychiat **22** 901, 1929

SYPHILITIC CORONARY ARTERITIS *

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CLEVELAND

Stenosis or obliteration of the ostia of the coronary arteries is generally recognized to be a common complication of syphilitic aortitis. In most of the standard textbooks and reference books of pathology, mention is made of frequent occurrence of this complication, and several authors have emphasized its clinical importance. Scott¹ recently stressed the significance of the coronary involvement in the relative incapacity of the heart for compensation in cases of syphilitic aortic insufficiency. MacKenzie² regarded coronary stenosis as one of the most common causes of sudden death from cardiac failure in syphilitic aortitis.

It is of interest that the various investigators of syphilitic vascular disease have almost without exception regarded the coronary involvement as being limited to that part of the coronary artery included in the wall of the aorta and the stenosis as being due to aortic rather than to coronary disease. The opinions expressed by Benda,³ MacCallum⁴ and Jores⁵ are that the coronary circulation is impaired by the periosteal intimal proliferation in the aorta, and that syphilis of the coronaries, per se, is rare or nonexistent.

Kaufmann⁶ stated that endarteritis of the coronaries occurs in the course of syphilitic aortitis and leads in some instances to total closure of the ostia of the vessels. Warthin⁷ also observed the occurrence of syphilitic thrombo-arteritis obliterans of the coronaries, but expressed the opinion that it is not of frequent occurrence. In three studies of

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2 MacKenzie, I. Syphilis of the Circulatory System, *Glasgow M. J.* **92**: 209, 1919.

3 Benda, C. Die Gefaesse, in Aschoff, Ludwig. *Pathologische Anatomie*, Jena, Gustav Fischer, 1923, vol. 2, p. 73.

4 MacCallum, W. G. A Text-Book of Pathology, Philadelphia, W. B. Saunders Company, 1925, p. 351.

5 Jores, L. Herz und Gefaesse, in Henke and Lubarsch. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1924, vol. 2, p. 668.

6 Kaufmann, E. *Lehrbuch der speziellen pathologischen Anatomie*, Berlin, W. de Gruyter & Company, 1922, vol. 1, p. 43.

7 Warthin, A. S. Syphilis of the Medium and Smaller Arteries, New York M. J. **115**: 69, 1922.

syphilis of the medium-sized vessels (Herxheimer,⁸ Turnbull,⁹ Saphir¹⁰), the coronary arteries are not considered as being the seat of syphilitic arteritis. Each of these investigators notes the frequent occurrence of stenosis or occlusion of the coronary orifices in syphilitic arteritis, but considers the change to be due to the disease in the wall of the aorta. In regard to aortic insufficiency, Scott stated: "In this connection it is interesting to note that in spite of the active disease surrounding the orifices, the coronary vessels themselves were seldom involved. When opened, they presented a smooth, normal intima."

A lesion of such vital clinical interest deserves thorough pathologic examination. Statistical studies have indicated that syphilitic aortitis occurs in 7 per cent of all cases coming to autopsy (Oberndorfer¹¹), and that in cases of syphilis the percentage of aortic involvement reaches 82 (Stadler¹²).

This study is not intended to represent a statistical investigation. Eight cases in which there was syphilitic aortitis with stenosis or obliteration of one or of both coronary arteries were selected for study. Representative blocks from various portions of the coronary arteries, myocardium, aortic valve and aorta were taken for histologic examination. Sections were stained with hematoxylin and eosin and by van Gieson's picrofuchsin, Saphir's orcein-hematoxylin and Waitlin-Starry's silver methods. The silver stains for spirochetes were controlled by sections of congenitally syphilitic liver in which spirochetes were readily identified.

REPORT OF CASES

CASE 1—W. M., a white man, aged 65, entered the hospital complaining of shortness of breath, nausea, vomiting and dependent edema. To within a few days before admission, the patient had been in good enough health to climb three flights of stairs to his room each day without assistance. There had been no previous symptoms of cardiac failure and no history of anginal attacks. The Wassermann reaction of the blood was ++++

His course in the hospital was one of progressive decline. There was no response to digitalis. He died on the ninth day of hospitalization. The clinical diagnosis was congestive heart failure and syphilitic aortitis with aortic insufficiency.

The pathologic diagnosis was chronic syphilitic aortitis, chronic syphilitic aortic valvulitis with insufficiency, chronic obliterative arteritis of the proximal portions and orifices of the coronary arteries, cardiac hypertrophy and dilatation,

8 Herxheimer, G. Zur Aetiologie und pathologischen Anatomie der Syphilis, *Ergebn d allg Path u path Anat* **11** 1, 1907.

9 Turnbull, H. M. Alterations in Arterial Structure and Their Relation to Syphilis, *Quart J Med* **8** 201, 1915.

10 Saphir, O. Involvement of the Medium-Sized Arteries Associated with Syphilitic Aortitis, *Am J Path* **5** 397, 1929.

11 Oberndorfer, J. Die syphilitische Aortenerkrankung, *Munchen med Wchnschr* **60** 505, 1913.

12 Stadler, E., cited by Kaufmann (footnote 6).



Fig 1 (case 1) —Stenosis of the proximal portion of the left coronary artery by chronic obliterative arteritis (three-fourths actual size)

chronic interstitial myocarditis, fatty degeneration of the myocardium, mural thrombosis of the right and left auricles, passive hyperemia of the lungs, liver, kidneys and spleen, and recent infarcts of the lungs

The heart weighed 590 Gm (fig 1). The hypertrophy was preponderantly of the left ventricle, with dilatation of all chambers. The myocardium was soft, flabby and pale grayish brown. The aortic valve was incompetent, with thicken-

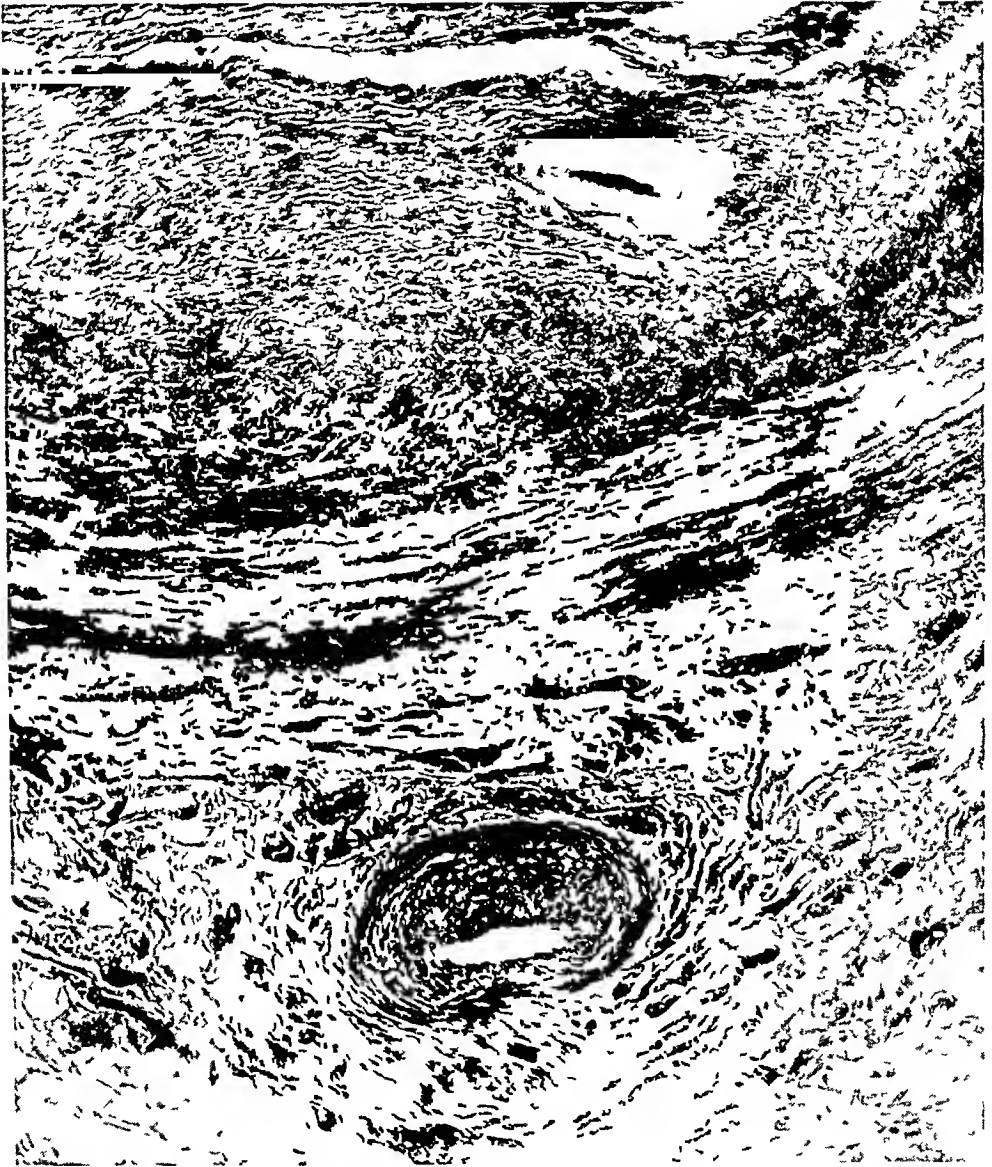


Fig 2 (case 1) —Obliterating endarteritis of vasa in the wall of the right coronary, $\times 160$

ing and shortening of the cusps and separation of the commissures. The aortic ring measured 9 cm in circumference.

The aorta was thin-walled and dilated. There was marked intimal sclerosis with formation of translucent, grayish-blue plaques and pitting and longitudinal wrinkling of the intima. There were many interruptions in the continuity of the media by fibrous scars, with irregularity in its thickness. The disease extended through the entire thoracic and most of the abdominal aorta.

The ostium of the right coronary artery was completely obliterated, and over its site was a thick, calcified, atheromatous plaque. For a distance of 1 cm from the aorta, the right coronary artery was represented by a solid fibrous cord, when this was sectioned transversely, the media appeared greatly thickened, and the lumen of the artery was occluded by what appeared to be intimal proliferation.

Histologic examination of sections through the first centimeter of the right coronary showed fairly well preserved media and dense fibrous adventitia, which



Fig 3 (case 1) —A vascularized, fibrous scar extending from the adventitia into the peripheral portion of the media of the left coronary, $\times 130$

was continuous with a wide zone of perivascular fibrosis. In the adventitia were a large number of vasa many of which were partially or completely obliterated by endarteritis (fig 2). There were many foci of lymphocytes and plasma cells, often of perivascular distribution. Occasional fan-shaped vascular scars extended into the media, with resulting disruption of elastic lamellae. The lumen of the vessel was completely obliterated by dense and, in places, calcified, fibrous connective tissue, in which occasional phagocytes containing blood pigment indicated that thrombosis had occurred.

The proximal 8 mm of the left coronary artery was stenosed, but not completely obliterated (fig 1). Its lumen over a distance of about 5 mm admitted the passage of a 1 mm probe with considerable resistance, and it did not seem likely that there was any considerable functional patency. The same microscopic changes (fig 3) were seen here as were described for the right coronary, except that there was less intimal proliferation and an absence of the complete obliteration of the lumen.

Except for a mild degree of intimal sclerosis in the ramus descendens of the left coronary, there were no other pathologic changes in the coronary system. No accessory or aberrant arteries could be demonstrated. The stomas of several large thebesian vessels in the left ventricle were identified macroscopically. An

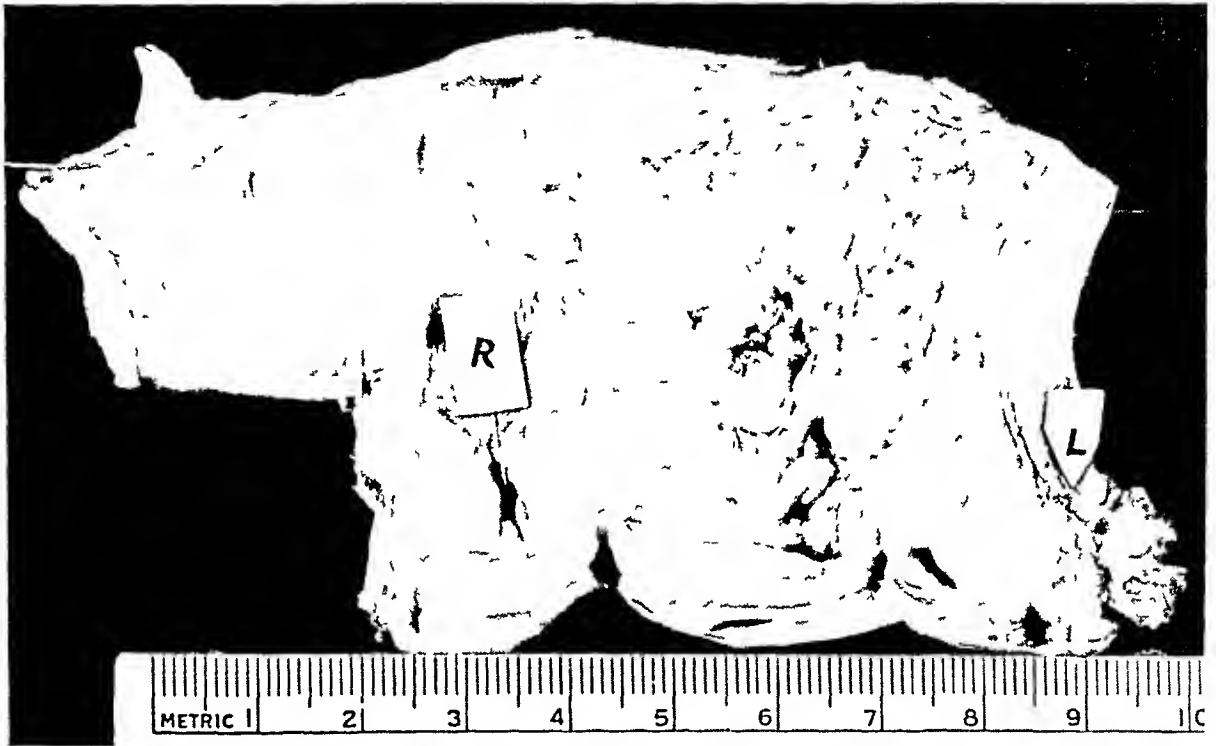


Fig 4 (case 2) —Proximal portion of the aorta, including the aortic valve. The right coronary is obliterated just distal to the aorta, the ostium being patent. The aortic portion of the left coronary is stenosed (actual size).

attempt was made by means of serial sections to demonstrate communication between the thebesian and the coronary circulation, but the series was inconclusive.

The myocardium was the seat of diffuse interstitial fibrosis, and throughout there were many small stellate scars not associated with exudation. In many areas, the fibrosis was perivascular and was the seat of myxomatous change. There was marked, generalized fatty degeneration of muscle cells.

Stains for spirochetes on sections of aorta, coronary arteries and myocardium were negative.

CASE 2—J. B., a white man, 44 years of age, was unconscious when admitted to the hospital. Just before admission, the patient had been seized with a sudden severe epigastric pain and loss of consciousness. There was no history of cardiac decompensation, but friends stated that the patient had complained of a similar

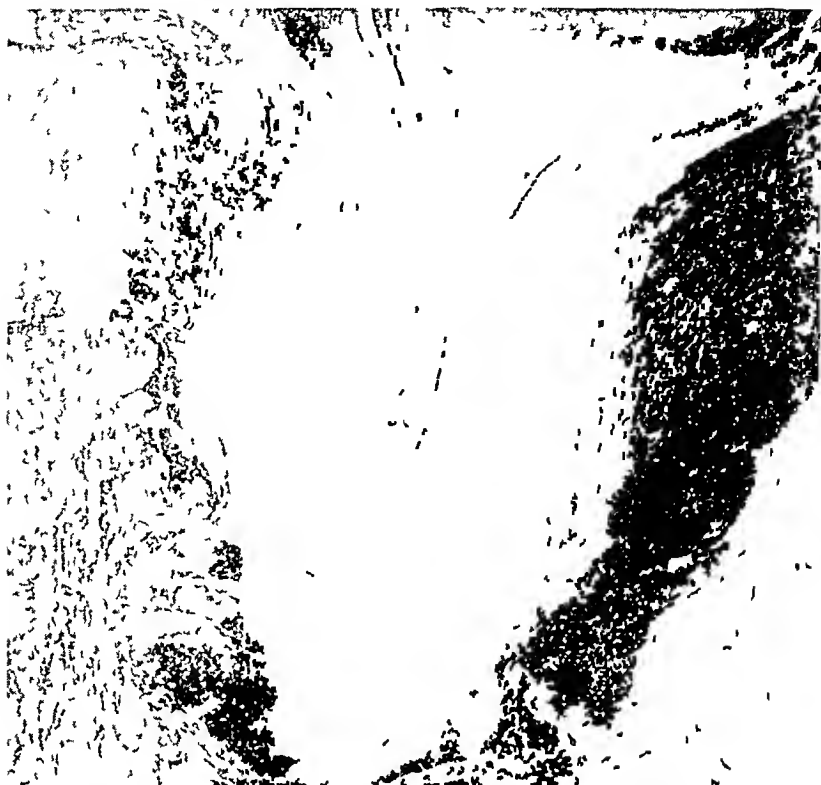


Fig 5 (case 2) —A tangential section through an obliterated segment of the right coronary artery distal to the aorta, elastic stain, $\times 12$

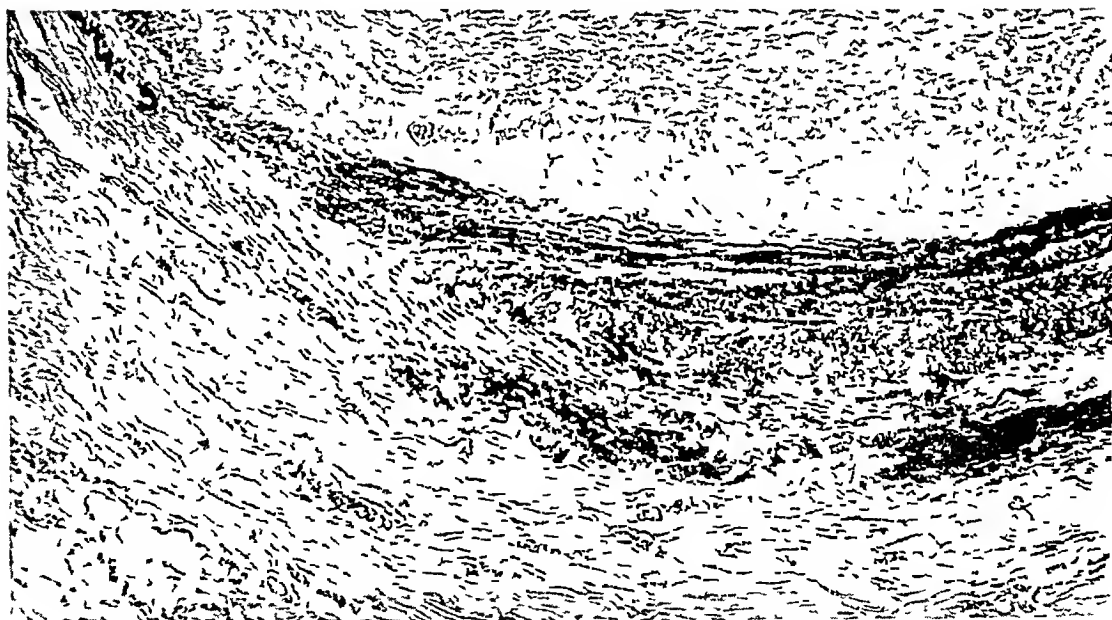


Fig 6 (case 2) —A section through the wall of the right coronary showing disruption of the elastica and intimal proliferation, elastic stain, $\times 110$

attack of epigastric pain and loss of consciousness a few week before. The patient died without rallying from the circulatory collapse. The clinical diagnosis was coronary thrombosis. No blood was taken for the Wassermann test.

The pathologic diagnosis was active syphilitic aortitis, active syphilitic aortic valvulitis, chronic obliterative syphilitic arteritis of the proximal portion of the right coronary artery, stenosis of the orifice of the left coronary artery, cardiac hypertrophy and dilatation, subacute fibrinous pericarditis, emphysema, pulmonary edema, healed gastric ulcer and healed pulmonary tuberculosis.

The heart was enlarged to 480 Gm, the hypertrophy being principally of the left ventricle. There was moderate dilatation of all chambers. The circumference of the aortic ring was 9 cm and of the ascending arch 9.4 cm. The wall of the aorta was greatly thickened, measuring 5 mm just above the aortic valve. Histologically there was a diffuse exudative, proliferative and degenerative inflammatory process involving the adventitia, media and intima, with formation of miliary gummas and large areas of granulation tissue. The change was typical of active syphilitic inflammation, with marked destruction of the wall of the aorta.

The leaflets of the aortic valve were only slightly shortened and thickened, with little commissural separation, and represented only a mild degree of insufficiency.

Both coronary ostia could be identified (fig 4). The right was a small saecular outpouching of the aortic wall, and just distal to the dilated orifice the artery was completely stenosed over a distance of about 6 mm.

Histologically (fig 5) there was a still intact endothelium-lined lumen, although it was not considered to be functionally patent. There were obliterating endarteritis of the vasa, perivascular infiltration of lymphocytes and plasma cells, with scarring of the media, and proliferation of the intima. The entire process was less active and presented more of the characteristics of chronicity than did the aortitis.

The orifice of the left coronary artery was reduced to a diameter of less than 1 mm, but the reduction continued only in that part of the artery which was included in the wall of the aorta. Distal to the aortic adventitia, the vessels showed no pathologic change. On microscopic examination, the coronary stenosis was found to be due to the surrounding productive inflammation in the aorta and not to disease of the coronary artery itself.

The myocardium, including branches of the coronary, showed no pathologic change other than some swelling and granularity of the muscle cells, with slight interstitial fibrosis.

Stains for spirochetes in the aorta were negative.

CASE 3—N. H., a Negress, aged 24, entered the hospital with a complaint of precordial pain, vomiting and weakness. Ten days before admission, she had a sudden sharp substernal pain, which was followed by vomiting. Otherwise the history was essentially negative. The only significant clinical observations were increased palpable cardiac activity with persistent systolic and diastolic murmurs. The pulse rate varied from 55 to 105, and the blood pressure averaged 122 systolic and 60 diastolic. She died suddenly during the night of her sixth day in the hospital. The clinical diagnosis was coronary or cerebral embolism. No Wassermann test was done.

The pathologic diagnosis was active syphilitic arteritis involving the thoracic aorta, both coronaries, the innominate, the left common carotid, the left sub-

clavian and the superior mesenteric arteries, and obliteration of the right, and stenosis of the left, coronary orifices

The heart weighed 280 Gm and presented no gross evidence of pathologic change. The aortic ring measured 7.5 cm in circumference, and the aortic valve appeared normal. The aorta beginning just above the ring and extending down to the diaphragm was greatly thickened, the wall measuring about 1.5 cm in thickness through the arch. The lumen of the aorta was reduced. The intima was smooth, but had a diffuse grayish-blue translucent appearance.

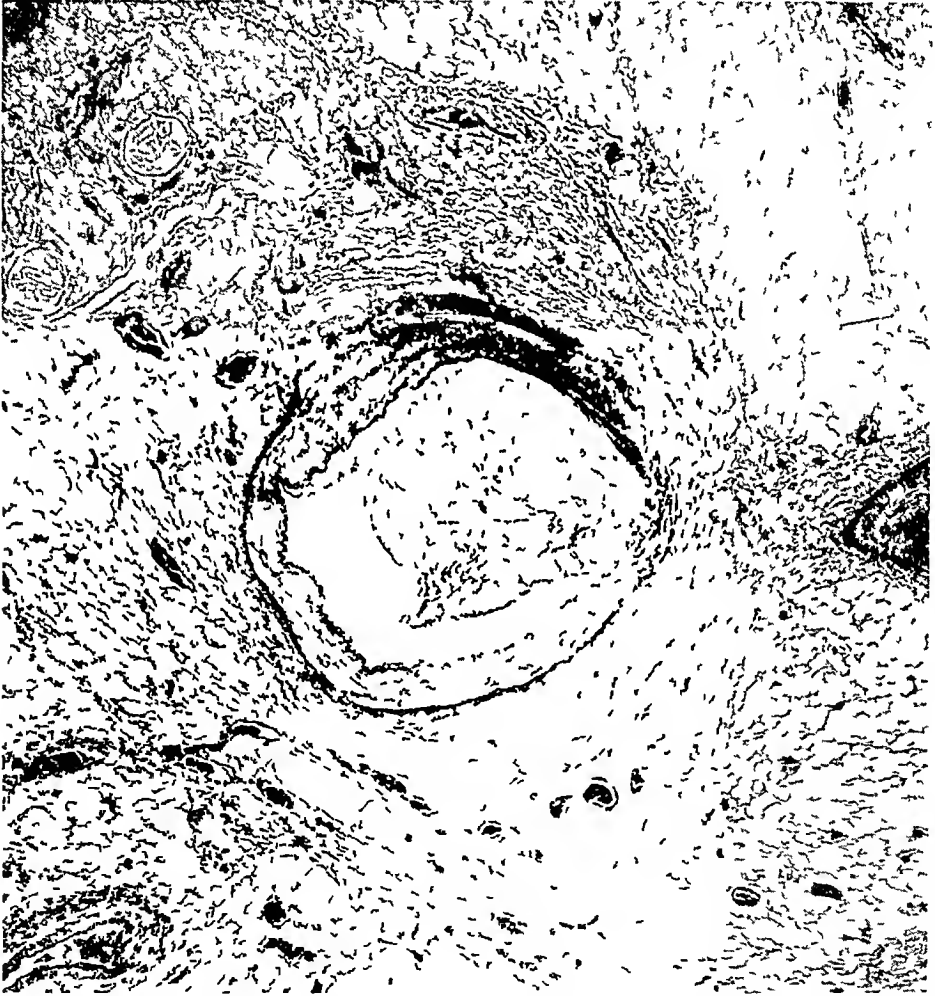


Fig 7 (case 3) —The proximal portion of the right coronary artery. The lumen is partially occluded by vascularized granulation tissue, which is continuous with fibrous proliferation in the media. Fragmentation of the elastica and proliferation of the adventitia are seen, elastic stain, $\times 18$.

Histologic examination of the aorta showed the intima to measure from 2 to 3 mm in thickness and to be, together with the superficial portion of the media, the seat of myxomatous degeneration. The media and adventitia were occupied by multiple foci of granulation tissue associated with the formation of new blood vessels, exudation of lymphocytes and endothelial cells, edema and small areas of coagulation necrosis with occasional giant cells. There was a marked obliterative endarteritis of the vasa.

The right coronary artery was completely obliterated for a distance of about 1 cm by what appeared grossly to be intimal proliferation.

Histologic examination of sections through the obliterated segment of the right coronary artery (fig 7) showed the lumen to be occluded by intimal proliferation.



Fig 8 (case 3) —Elastic stain showing encroachment of the media of the left coronary by vascularized, fibrous connective tissue, $\times 300$

The proliferated intima was vascularized and the seat of lymphocytic infiltration. The media was traversed by radially disposed, vascularized, fibrous scars often extending into the intima. There was marked disruption of the continuity of the elastica (fig 8). The vasa were the seat of an obliterative endarteritis, and in the adventitia and the wide surrounding zone of perivascular fibrosis there was marked exudation of lymphocytes and endothelial cells.

The left coronary artery admitted the passage of a small probe, but the patency of the lumen did not exceed a diameter of 1 mm. This reduction of patency extended for a distance of about 9 mm from the orifice. On microscopic examination there was found to be a gumma with a diameter of approximately 5 mm situated in the wall of the aorta immediately adjacent to the coronary

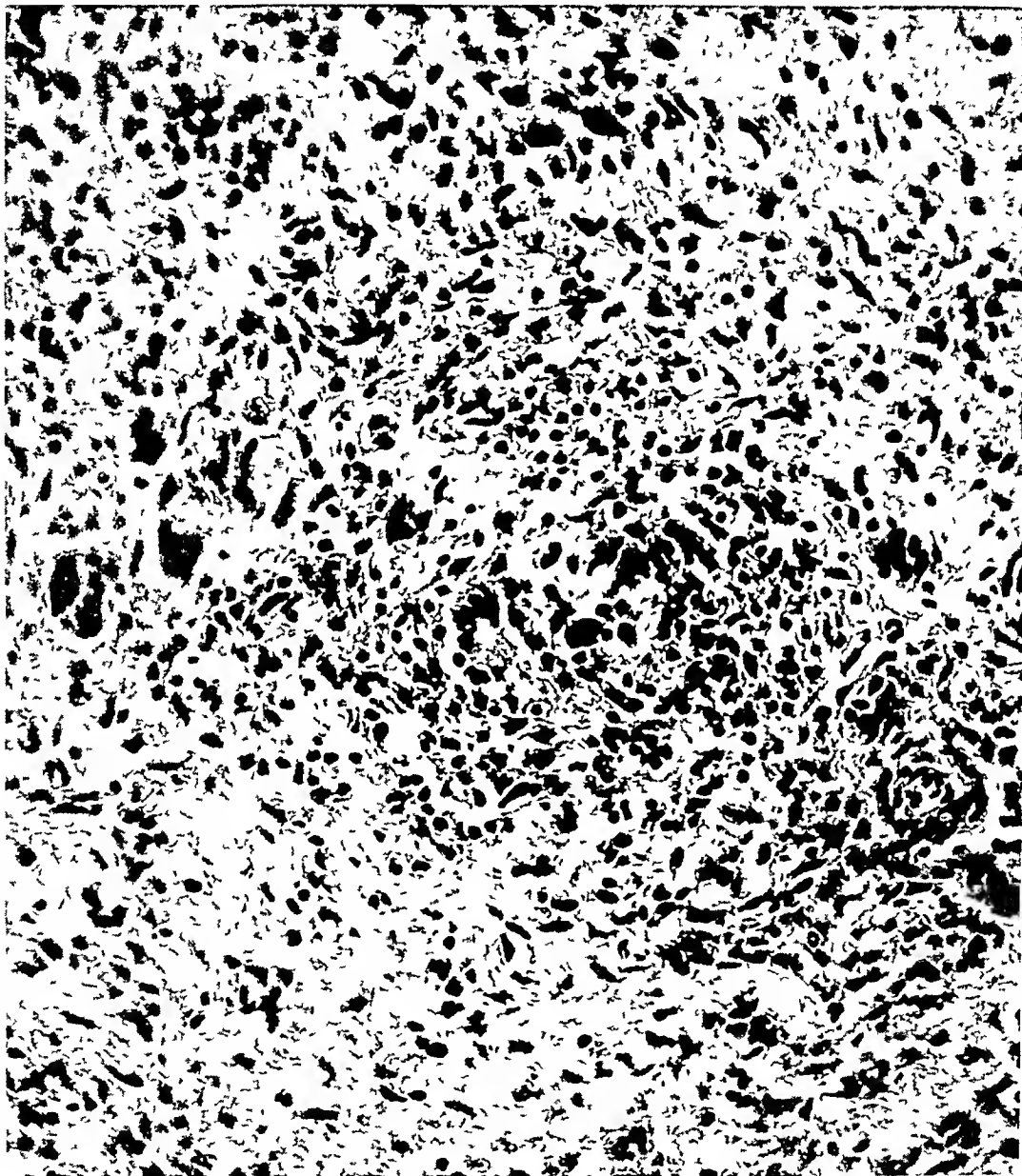


Fig 9 (case 3) —Peripheral exudative zone of a gumma that impinged on the left coronary ostium, $\times 500$

orifice (fig 9). This gumma had encroached on and compressed the coronary in its aortic portion. Distal to the aorta, extending as far as the stenosis, changes similar to those described for the right coronary, but without complete obliteration of the lumen, were present.

CASE 4—A H, a Negro, aged 55, was a cardiac invalid the last five years of his life. He had persistent hypertension, averaging 210 systolic and 130 diastolic. In five of his six periods of hospitalization, he was admitted with cardiac decompensation. Each time his heart was readily compensated on rest in bed and the administration of digitalis. There was no evidence of valvular heart disease or of aortitis, and the Wassermann reaction was negative. On the eighth day of the sixth hospitalization, the patient died suddenly from circulatory collapse. The clinical diagnosis was coronary thrombosis.

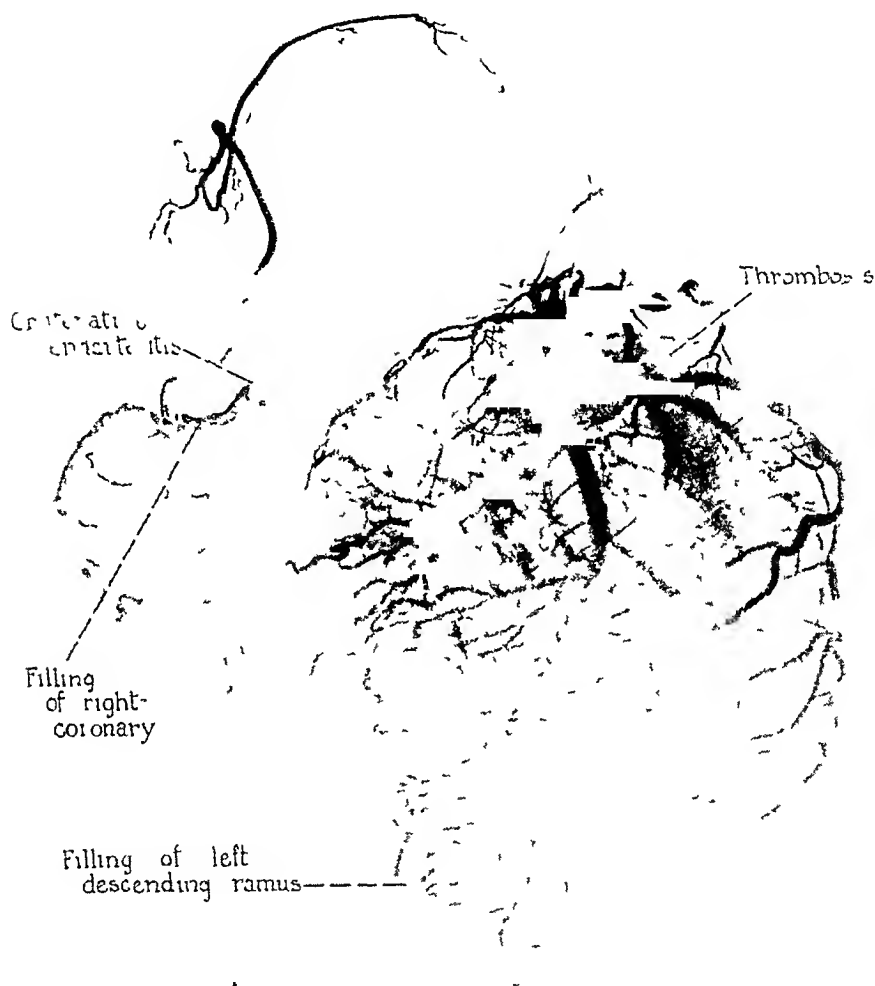


Fig 10 (case 4)—Roentgenogram of the heart injected through the left coronary orifice. There is complete obliteration of the proximal portion of the right coronary artery and thrombosis of the descending ramus of the left.

The pathologic diagnosis was thrombosis of the ramus descendans of the left coronary artery, chronic obliterative syphilitic arteritis of the proximal portion of the right coronary artery, cardiac hypertrophy and dilatation, chronic syphilitic aortitis, generalized, severe arteriosclerosis, mild arterioneurosclerosis, and generalized miliary tuberculosis.

Although active miliary tubercles were widely disseminated, their number was sparse, and they constituted an incidental microscopic observation.

The heart weighed 870 Gm, the hypertrophy being preponderantly of the left ventricle. There was little evidence of dilatation. The endocardium and the valves appeared normal. The aortic ring measured 8.8 cm. The leaflets were wide, deep and not thickened, there was no separation of the commissures. In the aorta there were two small saccular dilatations just above the aortic ring. There was pronounced intimal sclerosis throughout the entire aorta, with pitting, longitudinal scarring, formation of hyaline plaques and calcification. Histologically, the changes in the aorta were of a chronic nature, with obliterating arteritis of the vasa and medial scarring and degeneration, without prominent vascularization and with but little exudation. There was marked intimal sclerosis with calcification.

The lumen of the right coronary artery was occluded over a distance of about 1 cm. from its orifice, the latter being marked by a small dimple in the intima of the aorta. There was no reduction in the diameter of the vessel, even in its occluded portion, the obliteration being by fibrous proliferation into the lumen. Microscopic examination of the obliterated segment of the right coronary indicated a pathologic change of long duration, with partial calcification of the dense fibrous cicatrix that occupied the lumen of the vessel. The continuity of the elastic fibers of the media was interrupted by many small, dense, fan-shaped, fibrous scars radiating in from the adventitia. There were extensive hyalinization of the media and some perivascular lymphocytic infiltration of the media and adventitia.

The left coronary orifice was greatly distended, as was also the proximal 15 mm. The entire left coronary appeared unusually large, but there was neither gross nor microscopic evidence of syphilis of any portion. The major descending ramus of the left coronary was anomalous in its course and extended obliquely across the anterior surface of the left ventricle. The proximal segment of this artery was occluded by an organized thrombus, which was superimposed on a partially obstructive ulcerated atheromatous plaque. A 17 per cent suspension of bismuth oxychloride in water containing 10 per cent acacia was injected into the orifice of the left coronary artery at a pressure of 120 mm. of mercury. The injection was continued over a period of four hours and was preceded by perfusion of the heart through the left coronary with saline solution until the perfusing fluid was free from blood. After injection the vessel was tied, and roentgenograms were taken (fig. 10).

CASE 5—J. J., a Negress, aged 48 died during her first period of cardiac decompensation. Symptoms of heart failure became progressively more severe over a period of months, and her death followed a sudden circulatory collapse that occurred two weeks after admission. There was no response to strophanthin or digitalis during the last period of hospitalization. The clinical diagnosis was syphilitic aortitis with aortic valvular insufficiency and chronic myocarditis. The Wassermann reaction of the blood was +++.

The pathologic diagnosis was chronic syphilitic aortitis, aneurysm of the abdominal aorta, chronic syphilitic aortic valvulitis with insufficiency, chronic syphilitic arteritis of the proximal portions of the coronary arteries, cardiac hypertrophy and dilatation, chronic interstitial myocarditis, generalized arteriosclerosis and chronic passive congestion of the lungs, liver and spleen.

The heart weighed 520 Gm. Both chambers were dilated, and the myocardium was pale and tough. The aortic valve ring measured 10 cm. in circumference and was obviously incompetent. The commissures of the aortic valve were widened leaving spaces 2 to 3 mm. wide between the valve cusps. The left coronary cusp was shortened, thickened and rolled in.

There was a fusiform dilatation of the ascending arch of the aorta, which reached a maximum circumference of 13 cm. The wall was thin and the intima

sclerosed and calcified. Longitudinal wrinkling, pitting and vascularization of the intima were present, and there were elevated, translucent collars surrounding the stomas of the intercostal arteries.

Both coronary orifices were stenosed, the stenosis being most marked in the wall of the aorta. The walls of the proximal portions of both coronaries were thickened for a few millimeters distal to the aorta. The left coronary orifice measured 1.5 mm, and the right 2 mm, in diameter. The rest of the coronary arterial system appeared normal, save for a mild degree of intimal sclerosis.

Sections of both coronaries taken about 5 mm from their ostia showed little intimal proliferation and no degeneration or calcification of either media or intima. There was a considerable increase in adventitial fibrous connective tissue, and the vasa were the seat of marked intimal sclerosis, many of them being surrounded by lymphocytic infiltration. Occasional small vascularized radial scars extended into the media, with disruption of the elastica. Sections taken longitudinally through the orifice of the left coronary presented the same histologic changes with the addition of intimal proliferation and myxomatous degeneration of the media.

CASE 6—J. S., a Negro, aged 47, died during his second period of hospitalization for cardiac decompensation. There had been symptoms of cardiac failure over a period of nine months preceding his death. Electrocardiographic studies were not significant. The Wassermann reaction of the blood was +++++. Death was due to congestive heart failure, and a clinical diagnosis of syphilitic aortitis with aortic valvular insufficiency was made.

The pathologic diagnosis was active syphilitic aortitis, aneurysm of the abdominal aorta, with erosion of the tenth, eleventh and twelfth thoracic and first lumbar vertebrae, chronic syphilitic arteritis of the proximal portion of the right coronary artery, cardiac hypertrophy and dilatation, fatty degeneration of the myocardium, and mild arteriosclerosis.

The heart weighed 680 Gm, the hypertrophy being participated in by both ventricles, with moderate dilatation. The myocardium was soft and mottled with yellow. The aortic valve ring measured 8.5 cm in circumference and the valve leaflets were slightly thickened, with a suggestion of separation of the commissures. The wall of the aorta was generally thickened, measuring 4 mm just above the aortic ring. There was a fusiform dilatation of the arch, reaching a circumference of 9.75 cm, and a saccular aneurysm on the posterior surface of the abdominal aorta with partial destruction of the vertebrae enumerated in the pathologic diagnosis. Active syphilitic aortitis was recognized on gross and microscopic examination. There was a slight degree of stenosis of the orifice of the right coronary, the left appearing normal. Other than the stenosis that resulted from thickening of the aortic intima around the ostium, the coronaries appeared normal.

On histologic examination, the left coronary showed no abnormality but the proximal 6 mm of the right coronary was the seat of adventitial thickening, with an obliterating arteritis of the vasa, perivascular lymphocytic infiltration and small radial scars extending into the media.

CASE 7—A. G., a Negress, aged 55, died following a pulmonary hemorrhage from an abscess complicating organized lobar pneumonia. Her clinical history was negative so far as cardiovascular disease was concerned. The clinical diagnosis of syphilitic aortitis was made from the physical examination and from the +++++ Wassermann reaction.

The pathologic diagnosis was organized pneumonia with multiple abscesses, pulmonary hemorrhage into the abscess cavity with free blood in the bronchi,

trachea, mouth and stomach, chronic syphilitic aortitis, fusiform aneurysm of the aorta, chronic syphilitic aortic valvulitis, stenosis of the ostia of the coronary arteries, cardiac hypertrophy, and arteriosclerosis

The heart weighed 400 Gm and, except for the hypertrophy, was essentially normal. The aortic ring measured 8.5 cm in circumference, and the valve cusps were slightly thickened and rolled in, with beginning commissural separation. The aorta was moderately dilated in the ascending arch, and in the middle third there was a large saccular aneurysm. The intima of the entire aorta was thickened and puckered and contained hyaline plaques and vascularized depressed scars.

Both coronary orifices were stenosed, but they were still moderately patent. The stenosis was due entirely to intimal thickening around the ostia, and the vessels distal to the aorta showed no gross or microscopic evidence of syphilis.

CASE 8—J. J., a Negro, aged 37, entered the hospital in his fourth period of cardiac decompensation and died with a clinical diagnosis of syphilitic aortitis with valvular insufficiency, cardiac decompensation and bronchopneumonia. The Wassermann reaction of the blood was ++++. The autopsy confirmed the clinical diagnosis, and incidentally disclosed moderately severe stenosis of both coronary orifices due to the intimal proliferation and calcification in the aorta. As in the preceding case, the disease was limited to the ostia, the coronaries themselves showing no evidence of syphilis.

COMMENT

In six of the eight cases studied, the stenosis of the coronary arteries was due to, or contributed to by, syphilitic arteritis of their proximal portions. In none of these did the arteritis extend farther than the first 10 to 12 mm of the vessel. In some, the stenosis was at the orifice, while in others the orifice was patent and the stenosis was distal to the aorta. Active syphilitic coronary arteritis was present with chronic inflammation of the aorta, and in some cases the coronary disease was chronic while the aortic syphilis was active. The coronary disease was not in all cases associated with syphilitic aortic valvulitis. The course of the coronary arteritis as hypothesized from a comparison of the mild with the severe pathologic changes indicated that the vascular change began in the adventitia as an obliterative endarteritis with perivascular infiltration of lymphocytes and plasma cells and medial damage, progressing from the periphery in toward the lumen of the vessel. Some of the arteries with these mild changes were stenosed at their orifices by proliferation of the aortic intima.

In cases in which the proximal extra-aortic portion of the coronaries was stenosed, the stenosis was due to intimal proliferation. In some instances, the proliferated intima had the appearance of well vascularized granulation tissue infiltrated by lymphocytes, and the media was disrupted by exudative, vascularized granulation tissue, with considerable thickening of the adventitia (fig. 7). The end-stage of this coronary endarteritis was thrombosis of the narrowed lumen with organization and, in some instances, calcification of the obliterating thrombus.

In cases 1, 2 and 3, the immediate cause of death appeared to be an obliterative coronary arteritis. All three patients died following sudden cardiovascular collapse characterized clinically as coronary disease. Two of these three had preceding anginal attacks. Electrocardiographic studies were not significant so far as coronary disease was concerned, and histologic studies of the myocardium failed to disclose evidence of infarction. It seems probable that in cases 1 and 3 there had developed a collateral circulation which by exclusion must have been either through the thebesian or through the aortic periadventitial vessels. The latter was deemed improbable because no periadventitial vessels of sufficient caliber to supply the heart were found in the ascending arch. In both of these there was almost complete obliteration of both coronary ostia, and this obliteration, as judged from the histologic study, was of considerable duration. The reason for the failure of this compensatory circulation after its apparent functional competency was not disclosed. In case 3 (fig 9), the syphilitic inflammation was active with milium gummas and excessive proliferation of granulation tissue, so that it seems possible for the obliteration of this vessel to have been an acute phenomenon. Injection of the left coronary artery in case 4 (fig 10) indicated that the major coronary tree could be filled, although only the left orifice was patent and although the left descending ramus was thrombosed. The collateral circulation was adequate to fill the right coronary up to its obliterated orifice and to fill the recently thrombosed left descending branch below the point of obstruction. The injection mass, although too coarse to give capillary filling, was found free in the chambers, and no breaks in the continuity of the endocardium could be demonstrated. This observation was in accord with the investigations of Wearn¹³ and was considered to indicate the patency of coronary-thebesian communications.

SUMMARY

Stenosis and obliteration of the proximal portions of the coronary arteries by syphilitic endarteritis frequently complicates syphilitic aortitis. The syphilitic inflammation of the coronary is not limited to that part of the artery included in the wall of the aorta. The coronary endarteritis occurs independently of aortic valvulitis and in some instances is the immediate cause of death without preceding cardiac decompensation. In two of the cases reported, the coronary stenosis was so complete and was of such long duration as to necessitate the hypothesis of a collateral blood supply, presumably through the thebesian vessels. The cause of the failure of the collateral circulation was not demonstrated.

¹³ Wearn, J. T. The Role of the Thebesian Vessels in the Circulation of the Heart, *J. Exper. Med.* **47** 293, 1928.

"MALIGNANT NEPHROSCLEROSIS" (FAHR)

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AND

SADAO OTANI, M D

NEW YORK

The occurrence of cardiac hypertrophy in patients with contracted kidneys was recognized by Bright¹. A causal relationship however between vascular alterations (arterio-capillary fibrosis) and "chronic Bright's disease" was first maintained by Gull and Sutton². Years later, Ziegler³ showed the dependence of some forms of renal atrophy on the arteriosclerosis of the renal arteries (arteriosclerotic contracted kidneys). He however, still believed in the occurrence of a primary chronic interstitial nephritis with atrophy which he accepted to be the end-result of an inflammatory condition leading to a hyperplasia of the stroma. Jores⁴ deserves the credit for having shown for the first time that such forms of renal atrophy, at that time commonly called chronic interstitial nephritis were actually caused by arteriosclerosis of the smaller renal blood vessels. In Ziegler's form of renal arteriosclerosis, mainly the larger vessels were involved, though he mentioned the occasional occurrence of arteriosclerosis of the smaller vessels and even of the glomerular tufts. This distribution was bound to cause an irregular and focal type of cicatricial atrophy. According to Jores'⁵ new conception, however, the diffuse fine granular kidney in chronic interstitial nephritis was also vascular, atherosclerotic in origin. This type of renal atrophy was always found combined with a marked hypertrophy of the left ventricle and Jores pointed out that such cases were generally terminated by the vascular alterations (cardiac insufficiency or apoplexy). Furthermore, he gradually developed a point of view, already long held by Allbutt,⁶ that the excessive cardiac hypertrophy might be

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5 Jores, L. Ueber die Beziehungen der Schrumpfnieren zur Herzhypertrophie vom pathologisch-anatomischen Standpunkt, Deutsches Arch f klin Med **94** 1, 1908

6 Allbutt, Sir Clifford. Diseases of the Arteries Including Angina Pectoris, London, The Macmillan Company 1915, vol 1

produced by other than renal causes. Allbutt, recognizing the primary importance of hypertension in the causation of cardiac or cerebral failure stressed the distinction between "Bright's disease" and another malady (hypertensia) which "abuts upon cardiac defeat or apoplexy, and does not at any stage, even of a fatal career, present uremic symptoms." He apparently did not recognize or include cases of primary hypertension with renal insufficiency. The old authors, however (Traube,⁷ Bartels,⁸ Delafield⁹), had not failed to emphasize that the fatal issue in patients suffering from genuine contracted kidneys or chronic interstitial nephritis was oftener determined by cardiac failure or cerebral accidents than by renal insufficiency, but nevertheless they looked on the kidneys alone as the seat and cause of the morbid process. It is clear that such diametrically opposed views led to much confusion and were the source of constant disagreement between pathologists and clinicians.

The strict clinical differentiation between primary hypertensive conditions existing with and without renal insufficiency and the recognition of pathologic criteria of two types of vascular renal disease corresponding to these two clinical forms were first established by Volhard and Fahr.¹⁰ Whereas only arteriosclerosis was supposed to be associated with the simple or benign hypertension, a combination of arteriosclerosis with inflammatory renal changes was held to be responsible for a malignant form of hypertension, the "Kombinations Form." It was only logical to assume that this difference in morphology was the expression of a difference in etiology. Accordingly, a toxic factor was postulated by Volhard and Fahr which, superimposed on the arteriosclerosis of the small vessels produced the combination form.

Pathologists soon objected to this dualistic conception of vascular renal diseases. Thus, Paffrath¹¹ and Jores¹² assented to a differentia-

7 Traube, L. Ueber den Zusammenhang von Herz und Nierenkrankheiten, Berlin, A. Hirschwald, 1856.

8 Bartels, C. Handbuch der Krankheiten des Harnapparates, in von Ziemssen, H. Handbuch der speciellen Pathologie und Therapie, Leipzig, F. C. W. Vogel, 1877.

9 Delafield, F. On the Diseases of the Kidneys Popularly Called Bright's Disease, Lectures in the Practice of Medicine, New York, James T. Dougherty, 1904, pt. 4.

10 Volhard and Fahr. Die Bright'sche Nierenkrankheit, Berlin, Julius Springer, 1914.

11 Paffrath. Ueber die als "Kombinationsform" bezeichnete Nierenerkrankungen, Inaug. Diss., Marburg, 1916.

12 Jores, L. Warum schreiben wir der Sklerose der Nierenarteriolen eine Bedeutung für das Zustandekommen gewisser Formen von Schrumpfnieren zu? Virchows Arch. f. path. Anat. **223** 233, 1917.

tion into two clinical forms, but maintained that the anatomic pictures are identical, varying the one from the other merely in extent and distribution of the atherosclerotic process involving the small vessels. They believed that in the pure hypertensive forms there existed only a focal involvement of the arterioles by atherosclerosis, whereas in the renal form there was a diffuse distribution of the same process. Lohlein¹³ also, though recognizing the clinical distinction, did not see any essential morphologic and etiologic difference in the pathology. According to his conception, apparent variations in the histologic picture were explained adequately by differences in the severity of the atherosclerosis of the small vessels, and furthermore, the rate of development of this atherosclerotic process determined its severity. He wanted to designate this difference in degree and tempo by the terms arteriosclerosis initialis seu lenta et progressa. This term was not happily chosen. It enabled Fahr to point to the paradoxical fact that according to Lohlein's terminology the advanced lesions are found, as a rule, in younger persons, and the initial changes in the later phases of life. This relationship between the lesion and the age of the patient was clearly shown in Fahr's statistics and was confirmed by our material. In subsequent years, a number of papers from the clinical and pathologico-anatomic standpoints were published along the lines developed by Volhard and Fahr (Umber,¹⁴ Rosenthal,¹⁵ Herxheimer,¹⁶ Machwitz and Rosenberg¹⁷). The clinicians generally accepted the dualistic conception of hypertensive disease. The anatomists, however, usually rejected the pathogenic separation of the renal lesions. The postulated inflammatory changes of the glomeruli in the combination form were the main point of disagreement. Since 1918 Volhard¹⁸ has changed his ideas and no longer believes in the inflammatory nature of the glomerular and vascular changes. He now considers these lesions as the result of a prolonged

13 Lohlein, M. Zur Pathogenese der vascularen Schrumpfnieren, *Med Klin* **12** 741 and 872, 1916, Ueber Schrumpfnieren, *Beitr z path Anat u z allg Path* **63** 570, 1917, Erwiderung auf T. Fahr's Aufsatz, *Centralbl f allg Path u path Anat* **28** 209, 1917.

14 Umber. Richtlinien in der Klinik der Nierenkrankheiten. Berlin klin Wchnschr **47** 1261, 1916.

15 Rosenthal, K. O. Zur Frage der benignen und malignen Arteriosklerose der Nieren, *Deutsches Arch f klin Med* **133** 153, 1920.

16 Herxheimer, G. Nierenstudien I, *Beitr z path Anat u z allg Path* **64** 297, 1918.

17 Machwitz, H., and Rosenberg, M. Zur Klinik der vascularen Schrumpfnieren, *Deutsch med Wchnschr* **42** 1188, 1916, Klinische und funktionelle Studien uber Nephritis, *Munchen med Wchnschr* **63** 1285, 1916.

18 Volhard, F. Die doppelseitigen hematogenen Nierenerkrankungen, Berlin, Julius Springer, 1918.

ischemia caused by a permanent vascular spasm Fahr¹⁹ also minimized the importance of the inflammatory glomerular alterations and instead stressed the inflammatory vascular damage. In a comprehensive article,²⁰ he emphasized far more the vascular lesions designated as necrotizing arteriolitis, productive endarteritis and periaarteritis than the glomerular changes that serve as criteria in the differential diagnosis between benign and malignant nephrosclerosis. This emphasis on the significance of characteristic arterial lesions as a basis for the morphologic distinction and for the pathogenesis of vascular nephrosclerosis with and without renal insufficiency clears the way for a possible agreement between Fahr and his opponents. These (Hersheimer,²¹ Stern²² and Meyer²³) recognized the peculiar arteriolar necrosis in several cases with renal insufficiency as a factor for differentiation. On the other hand there still exists a strong difference of opinion between Fahr and the opposite school in the matter of a specific etiology (syphilis, lead or articular rheumatism). However, some agreement has been reached. Hersheimer²⁴ recognized the possibility of a toxic damage superimposed on the original atherosclerosis leading to the severe picture of arteriolar necrosis. In this connection, it is well to remember that Lohlein, the strongest opponent of Fahr, recognized arteriolar necrosis and published an excellent picture of the condition²⁵.

Within the last few years we have had the opportunity to observe a number of pertinent cases. We believe that a critical investigation of their clinical and anatomic features may still contribute some points to clarify the disputed problems of pathogenesis.

19 Fahr, T. Kurze Bemerkungen zur Frage der malignen Nierensklerose, *Centralbl f allg Path u path Anat* **28** 408, 1917, Ueber maligne Nierensklerose (Kombinationsform), *ibid* **27** 481, 1916, Ueber Nephrosklerose, *Virchows Arch f path Anat* **226** 119, 1919, Ueber atypische Befunde aus den Kapiteln des Morbus Brightii nebst anhangswweisen Bemerkungen zur Hypertoniefrage, *ibid* **248** 323, 1924.

20 Fahr, T., in Henke and Lubarsch. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1925, vol. 6.

21 Hersheimer, G. Ueber Arteriolenekrose der Nieren, *Virchows Arch f path Anat* **251** 709, 1924.

22 Stern, M. Ueber einen besonders akut verlaufenen Fall von Arteriolenekrose der Nieren mit dem makroskopischen Bilde der "Grossen bunten Nieren," *Virchows Arch f path Anat* **251** 718, 1924.

23 Meyer, O. Ueber die Veränderungen und Bedeutung entzündlicher Gefässveränderungen in der Nieren mit besonderer Berücksichtigung der Glomerulitis der sekundären und genuinen Schrumpfnieren, *Verhandl d Deutsch path Gesellsch* **19** 352, 1923.

24 Hersheimer, G. *Krankheitslehre der Gegenwart*, Leipzig, Theodor Steinkopf, 1927, p. 182.

25 Lohlein (footnote 13, second reference).

MATERIAL AND METHODS

Our material consists of cases that in clinical course and pathologic picture conform with the diagnostic criteria of "malignant nephrosclerosis." In addition, we have examined a considerable number of cases of simple benign sclerosis, three cases of periaarteritis nodosa and cases of subacute glomerulonephritis with severe vascular lesions, we have also studied ample control material dealing with various questions of vascular pathology. Paraffin as well as frozen sections were used. The former were examined in long serial sections in order to obtain information about the status of the various portions of the vascular tree in the renal cortex. Various staining methods were employed, including the methods recommended by McGregor²⁶ for minute study of the glomeruli. Because of the similarity of the cases in clinical and anatomic aspects we shall describe in detail only a few typical cases and supply short notes on the others.

REPORTS OF CASES

CASE 1—*History*—M. F., a white man, aged 29, married, a garage manager, was first admitted to Mount Sinai Hospital on June 18, 1929. His mother had died of gallbladder disease. His father, three brothers, one sister and two maternal aunts, who were living and well, showed normal blood pressure and normal hearts. The patient had been married four years and had one child, aged $2\frac{1}{2}$ years. His wife never had had a miscarriage.

As a child he had had mumps. Eight years before admission to this hospital he had had his tonsils removed, six years later, he had had an appendectomy for acute appendicitis, and at this time his blood pressure was found to be 140 mm of mercury. Four years before admission, he began to have headaches two or three times a month. In August, 1928, the headaches became more severe and localized above the eyes and in the region of the temples. On advice of a doctor, the septum was corrected, but without relief. In October of the same year, he applied for life insurance and was refused because of high blood pressure (170 mm of mercury).

The headaches became continuous and severe, and on March 26, 1929, after having consulted many physicians, who treated him for sinus disease, he went to the hospital of the Rockefeller Institute, where he stayed until May 10. On admission there, his blood pressure was 240 systolic and 140 diastolic, it gradually fell to 215 systolic and 145 diastolic. Following a rather large hemorrhage from the rectum, the blood pressure fell to 155 systolic and 105 diastolic, but gradually rose again until at the time of his discharge from that hospital it was 180 systolic and 125 diastolic. Chemical examination of the blood at this time showed 22.7 mg of urea and 32 mg of nonprotein nitrogen per hundred cubic centimeters of blood. No dilution or concentration tests were done. The phenolsulphonphthalein excre-

26 McGregor L. The Finer Histology of the Normal Glomerulus, *Am J Path* 5:545, 1929.

*Drs. G. Baehr, L. Kessel, B. S. Oppenheimer and I. Strauss permitted us to use the clinical data in these cases, and Dr. R. L. Cecil, some of the clinical data in case 2.

tion was 60.3 per cent after two hours. The result of the urea clearance test (van Slyke index) was 45 per cent of normal. The diagnosis was arterial hypertension and chronic sinusitis. The patient was restricted to a low protein and salt diet, and thereafter felt better.

Because it was thought that the hypertension might be due to the sinus infections he was admitted to the New York Eye and Ear Infirmary, where a radical operation was performed on the right antrum. He had no relief from his headaches. On June 18, he fainted and was taken to Mount Sinai Hospital for observation.

Examination—The patient was an afebrile, poorly nourished young man, who had lost about 50 pounds (22.7 Kg.) within the last year. The heart was slightly enlarged to the left, the sounds were regular and strong. The blood pressure was 230 systolic and 172 diastolic. The eyegrounds on both sides revealed neuroretinitis.

The specific gravity of the urine was 1.010, a trace of albumin was shown, the sediment contained hyaline casts and a few red and white blood cells. The result of the concentration test was from 1.012 to 1.014. The phenolsulphonphthalein excretion was 57 per cent after two hours. Chemical examination of the blood showed urea nitrogen, 14 mg., uric acid, 16 mg., cholesterol, 162 mg., and sugar, 79 mg., per hundred cubic centimeters of blood. The Wassermann reaction was negative. The blood count gave hemoglobin, 102 per cent, red blood cells, 4,800,000, and white blood cells, 13,000, with polymorphonuclear leukocytes, 83 per cent, and lymphocytes, 17 per cent.

Course—During his stay in the hospital, the patient had a short attack of dizziness. A tentative diagnosis of malignant hypertension without nitrogen retention, with inability to concentrate the urine, was made. After a week the patient left the hospital and was admitted to Montefiore Hospital, as having a chronic case, for further study. There he stayed until August, 1929, without any change in his condition and without any new developments in the results of the laboratory tests. After leaving Montefiore Hospital, he was apparently better for two weeks, then his headaches recurred with great intensity. He became somewhat dyspneic and restless and vomited several times. He also noticed some diminution of vision and had many episodes of blurring.

On September 30, he again entered Mount Sinai Hospital. He was afebrile, drowsy and apathetic, and complained of severe headache. The breath was foul, but not urinous. The fundus presented marked hypertensive retinitis. The heart seemed slightly enlarged to the left. The second aortic was greater than the second pulmonic sound. There was a systolic murmur behind the middle of the sternum and over the aortic area and a systolic blow over the apex. No pericardial rub was heard.

On October 1, the blood pressure was 188 systolic and 134 diastolic. Chemical examination of the blood showed urea nitrogen, 14 mg., creatinine, 1.5 mg., uric acid, 2.8 mg., cholesterol, 248 mg., and sugar, 98 mg. On October 2, the result of the concentration test was from 1.010 to 1.016. The urine showed albumin (++) , many hyaline and granular casts and sparse red and white blood cells. For two weeks the condition remained the same.

On October 14, edema of the lower limbs was noted. The urine showed increased albumin and for the first time the guaiac reaction was positive. Chemical examination of the blood showed 30 mg. of urea nitrogen. In the evening, the patient suddenly became delirious, completely disoriented and uncontrollably restless. Under markedly increased tension, 50 cc. of clear fluid was withdrawn.

from the spinal canal. An intravenous injection of 2 cc of diallyl-barbituric acid was without effect, but after 8 minims (0.5 cc) of Magendie's solution was added, the patient became quiet. Within the next weeks, the blood pressure remained high, and precordial pains began. The urea nitrogen of the blood rose to 44, 57 and 109 mg per hundred cubic centimeters. On November 30, a loud friction rub was heard over the pericardium. The liver was enlarged and tender. Muscular twitchings developed, and the patient became stuporous. He died on December 7, sixty-eight days after his second admission and fifty-three days after urea retention had been ascertained the first time.

Necropsy—Necropsy was performed by Dr. Otani twelve hours later. The body was that of a poorly nourished white man in complete rigor mortis. The mucous membranes were pale and slightly cyanotic. No jaundice, petechiae or edema was present.

The lower lobe of the left lung showed a few scattered areas of grayish infiltration. The trachea and the larger bronchi were congested and contained mucopurulent exudate.

The heart with the ascending aorta weighed 550 Gm. The pericardial surfaces were dull, showed injection and were covered with fibrin. The left ventricular wall was enlarged, measuring as much as 3 cm on cross-section. The valves were thin and closed well. The pulmonary artery was smooth. The aorta showed a few scattered yellowish flecks in the intima, but was elastic. The coronary arteries also showed a few lipid deposits in the intima, but no narrowing. The myocardium of the left ventricle was yellowish gray.

The kidneys weighed 120 Gm each. They measured 11 by 5 by 3 cm. The capsules stripped easily, revealing a grayish brown-red surface. The red color was more prominent on the convexity, whereas the anterior and posterior surfaces appeared more grayish brown. The red portions were slightly depressed, and the surface was accordingly slightly granular like Scotch grain leather. There were numerous sharply circumscribed hemorrhages varying in size from that of a pinpoint to that of a pinhead. On section, the cortex was of equal width and sharply demarcated from the medulla. The regular markings were somewhat indistinct because of numerous irregular grayish flecks and larger, more sharply outlined dark red areas. Occasional hemorrhages like those on the surface were seen. The medulla showed radial striae running toward the papillae. The pelvis had numerous confluent hemorrhages. The intima of the renal artery was smooth. The kidneys are shown in figures 1 and 2.

Microscopic examination showed the surface of the kidneys to be slightly irregular, the capsule was neither thickened nor infiltrated by cells. On examination of the cortex under very low power magnification, the cortical structure was seen to be altered by a widespread increase in the stroma. The loose connective tissue infiltrated the parenchyma, separating and compressing the convoluted tubules, which only rarely formed islands where canaliculi were close to each other (fig. 3). The stroma was slightly infiltrated by lymphocytes, polymorphonuclear leukocytes, polyblasts and plasma cells. It contained a great number of dilated and engorged capillaries. The tubules often showed marked alterations. A great number, though separated by connective tissue strands, still retained their topographic histologic characteristics, but were dilated and contained hyaline casts, epithelial cells and debris, and red and white blood cells. Others, however, had an atrophic epithelial lining containing fat droplets, which were often doubly refractile, and hyaline droplets. The medulla showed a moderate increase in the stroma, the tubuli recti contained desquamated cells, cellular debris and hyaline casts. On examination of the malpighian corpuscles, one was surprised to find that only a

small number showed readily recognized damage as, for example, hyalinization (fig 3). The majority under low magnification appeared unaltered, except that their capillaries were completely or partially bloodless and were conspicuously small.

On higher magnification, one recognized a collapse of many tufts. The basal membrane of the capsule often showed slight hyalinization, and the external epithelial layer was occasionally conspicuous owing to an increase in the number of cells, which rarely contained fat but occasionally contained hyaline droplets. The changes of the internal epithelial layer in a relatively small number of glomeruli were far more conspicuous. They consisted in a multiplication of the

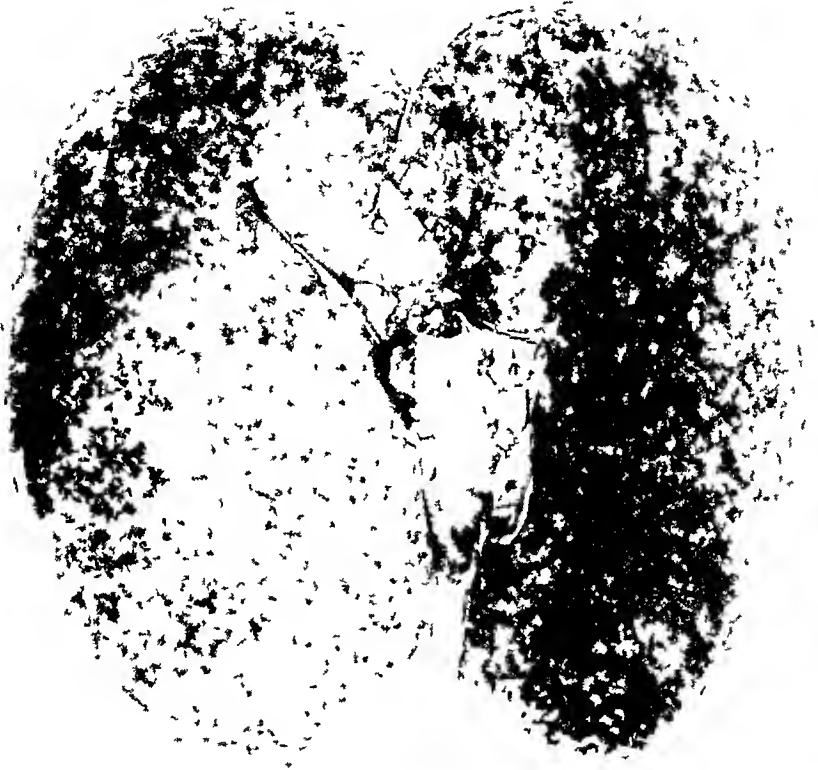


Fig 1 (case 1) —A kidney showing diffuse flat granulation but only slight decrease in size. Note the numerous hemorrhages.

cells covering the collapsed capillary loops, with frequent hyaline droplet degeneration and accumulation of isotropic and anisotropic fat droplets. Sometimes the entire glomerulus was infiltrated with fat. In paraffin sections, such loops were thickened and homogeneous and contained many vacuoles. The endothelial nuclei were pale, small and often broken up. The epithelial cells were large and swollen, frequently showing severe hyaline droplet degeneration and necrosis. The lumen of such capillaries was often thrombosed. Fusion of loops to each other and the capsule was not uncommon. The "arcuate arteries" and the large proximal branches of the interlobular arteries showed marked thickening of the intima. The media was often compressed. The internal elastic membrane was separated into several layers, between which there was a more or less cellular connective tissue. This showed a moderate number of fat droplets within and

between the fibroblasts. The adventitia was free from cellular infiltration. The more peripheral portions of the interlobular arteries showed an extreme degree of narrowing of the lumen caused by a proliferation of the subendothelial intimal layer, which formed a moderately cellular connective tissue with abundant fat infiltration. Lamellation of the internal elastic layer was less distinct in the peripheral portions of the vascular tree. The arteriolar endings of the interlobular arteries and the vasa afferentia showed diffuse fat infiltration and hyalinization with frequent nuclear disintegration, hemorrhagic infiltration of the wall, aneurysmic dilatation and perforation, and perivascular hemorrhage. Never, however, was infiltration with polymorphonuclear leukocytes or other inflammatory cells seen.



Fig 2—Cross-section of the kidney shown in figure 1, showing the diffuse grayish infiltrations that obscure the cortical markings

The heart showed fibrinous pericarditis. There were no changes in the arteries. Hypertrophy of muscle fibers was found.

The lung showed focal pneumonia. There was no excessive number of pigment cells. The alveolar septums were not thickened, and there was no evidence of chronic congestion.

The spleen disclosed considerable atherosclerosis of the larger vessels and a moderate degree of hyalinization of the arterioles.

The liver disclosed slight atherosclerosis of the larger vessels and insignificant hyalinization of the arterioles.

The pancreas presented moderate atherosclerosis and hyalinization of arterioles.

In the stomach and intestines, the arteries were normal

The prostate and seminal vesicles showed severe atherosclerosis of the larger arteries and hyalinization of the arterioles

In the muscle and skin, the arteries were normal

Diagnosis—The diagnosis was malignant nephrosclerosis, hypertrophy of the left ventricle, fibrinous pericarditis, acute hemorrhagic bronchitis, broncho-pneumonia of the left lower lobe, hypertrophy of the median lobe of the prostate, and hypertrophy and dilatation of the bladder

CASE 2—History—H. G., a white man, aged 42, married, a metal worker, was admitted to Mount Sinai Hospital on Aug 7, 1928. The family history was

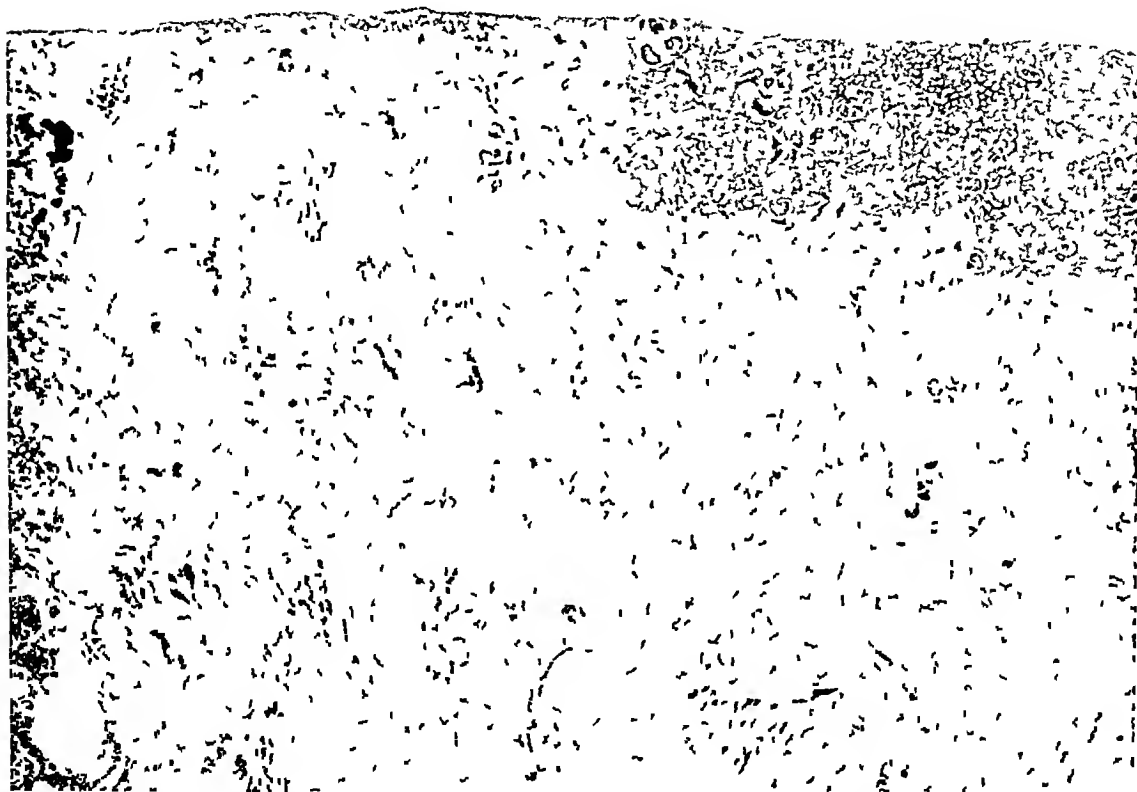


Fig 3 (case 1)—Low power view of the cortex showing the alteration of the normal structure: increase in the stroma, separation and atrophy of the tubules, but only sporadic hyaline glomeruli

unimportant. The patient had measles as a child and diphtheria in 1916. He had not had scarlet fever, rheumatism or frequent sore throats. He used no alcohol; he smoked cigars.

Three and one-half years before admission to the hospital, he was refused life insurance because of high blood pressure. At this time he had dyspnea and was examined at Cornell Clinic. The blood pressure was 178 systolic and 110 diastolic. The specific gravity of the urine was 1.028. No albumin or sugar was found. The result of the concentration test was from 1.021 to 1.031. The phenolsulphonphthalein excretion was 45 per cent after two hours. The diagnosis was essential hypertension.

Two years before admission, the blood pressure was 200 mm of mercury. Occasional ringing was present in the ears. In March, 1927, the blood pressure was 235 mm of mercury. At this time, sugar was found in the urine. The patient was put on a restricted diet, and the sugar disappeared. He had no polyuria. He received iodine, but this treatment was discontinued because of swelling of his neck. About eleven weeks before admission, his doctor noticed that the liver was enlarged and tender and that the heart was large. For ten weeks the patient had been suffering from attacks of dyspnea. He lost 28 pounds (12.7 Kg). Digitalis was given. Because of his symptoms he was admitted to the hospital.

Examination—The patient was afebrile. The blood pressure on admission was 220 systolic and 100 diastolic, during the next month it was between 220 systolic and 110 diastolic and 266 systolic and 135 diastolic. The left side of the heart was markedly enlarged. The fundi showed progressive neuroretinitis.

The urine showed albumin, many white, and rare red blood cells, and granular casts. The specific gravity was fixed at from 1.006 to 1.010. The phenolsulphonphthalein excretion after two hours was 10 per cent. The urea nitrogen of the blood, on admission, was 47 mg per hundred cubic centimeters. Uric acid was 4.2 mg. The Wassermann reaction was negative. The blood count gave hemoglobin, 50 per cent, red blood cells, 2,600,000, and white blood cells, 9,800. The differential count gave polymorphonuclear leukocytes, 79 per cent, lymphocytes, 21 per cent, mononuclears, 6 per cent, eosinophils, 1 per cent, and basophils, 1 per cent.

Course—On August 18, the patient began to vomit, and displayed general nervousness and anxiety. He suffered from precordial pain. The urea nitrogen of the blood was 78 mg. On September 7, there was a pericardial friction rub. The urea nitrogen of the blood was 106 mg. On September 10, there was uncontrollable vomiting. The urea nitrogen of the blood was 206 mg. The patient showed extreme emaciation. There were signs of bronchopneumonia in the left lower lobe. On September 12, the patient died. The clinical diagnosis was chronic glomerulonephritis with hypertension, pericarditis and uremia.

Necropsy—Necropsy was performed by Dr. Klemperer on the day of death. The kidneys weighed 120 Gm each, and measured 11 by 5 by 3 cm. They had a slightly granular surface and were a mottled grayish brown-red. They were firm. Numerous small hemorrhages were seen. The cortex was of normal width, and its markings were somewhat indistinct. The renal artery was very thick, as were also its ramifications.

Microscopic examination of the kidneys showed considerable increase in stroma, partial obliteration of cortical structure due to extensive tubular atrophy, insignificant glomerular fibrosis with diffuse capillary collapse, focal degeneration and proliferation of glomerular epithelium, occasional necrosis of capillary tufts and hemorrhagic infarction of the glomeruli, diffuse intimal proliferation within the entire vascular tree of the cortex, with elastic lamellation and fatty infiltration of the intima, excessive fatty changes and occasional necrosis of the arterioles without inflammatory reaction, an extreme degree of stenosis, and an occasional complete closure of small arteries and arterioles.

The heart presented severe myocardial fibrosis and recent myomalacia with lymphocytic infiltration. There was severe sclerosis of the coronary artery. The small intramyocardial branches were not involved. The aorta showed severe atherosclerosis.

Atherosclerosis of the arteries and hyalinization of the arterioles was shown to a marked extent by the pancreas, and the suprarenal glands, to a moderate extent by the spleen and to a slight extent by the stomach and intestines

The choroid showed extreme intimal proliferation of the small arteries

Diagnosis—The diagnosis was malignant nephrosclerosis, coronary closure (right posterior descending ramus), acute fibrinous pericarditis, hypertrophy of the left and right ventricles, myocardial fibrosis, atherosclerosis of the aorta, focal pneumonia of both lower lobes, and left hydrothorax

CASE 3—History—S. T., a white boy, aged 8½ years, was admitted to Mount Sinai Hospital on June 14, 1928. The family history was irrelevant. The patient had had whooping cough, pneumonia and measles. At the age of 3, he had suffered from nausea, vomiting, chills and convulsions for two weeks. The condition was diagnosed as ptomaine poisoning. There had been a second attack, but the date of this could not be ascertained. The patient had frequent colds. Within the last year, he became dyspneic on exertion. About three months prior to admission, it was observed in school that the child had difficulty with his eyesight. The diminution of vision was progressive. Severe headaches set in. On May 28, ophthalmologic examination revealed early retinitis. On June 6, the urine gave a strongly positive reaction for albumin. The blood showed urea nitrogen, 67 mg, uric acid, 72 mg, creatinine, 15 mg, per hundred cubic centimeters. In the last three weeks before admission, he vomited several times.

Examination—On admission, the patient was subacutely ill, but afebrile. He was not irrational, but acted queerly. There was a urinous odor of the breath. The heart was not enlarged. The second aortic beat was accentuated. The fundi showed extensive neuroretinitis with bilateral detachment of the retina. The blood pressure was 235 systolic and 175 diastolic.

The result of analysis of the urine for albumin was strongly positive, there were granular casts. The specific gravity was from 1.002 to 1.008. The phenol-sulphonphthalein excretion was represented only by traces. The urea nitrogen of the blood was 56 mg on admission, rising within the next few weeks to 110 mg to reach finally 235 mg per hundred cubic centimeters. Uric acid was 55 and 93 mg, cholesterol, 260 and 290 mg. The Wassermann reaction was negative. The blood count gave hemoglobin, 62 per cent, red blood cells, 3,510,000, and white blood cells, 11,800.

Course—During his stay in the hospital, the child was drowsy, had severe headaches and was nauseated. He had epistaxis, and he lost a great quantity of blood by rectum. He went gradually downhill. General convulsions developed. Within the last thirty hours, complete anuresis existed. Small purpuric spots developed. He died three weeks after admission.

Necropsy—Necropsy was performed fourteen hours later by Dr. S. Otani. The kidneys weighed 60 and 40 Gm, respectively. One was 7 by 4 by 1.5 cm, and the other was 6 by 3 by 1.5 cm in size. The surfaces showed diffuse flat granular elevations of irregular size. The color was brownish red. Numerous petechial hemorrhages were seen on the surface, and on cross-section. The cortical markings were indistinct, the separation of cortex and medulla was not sharp. The blood vessels were slightly thickened.

Microscopic examination revealed diffuse increase of the stroma and focal infiltration with lymphocytes and fibroblasts. No fat was seen. Numerous smaller and larger anemic infarcts were seen, with complete necrosis of tubules and glomeruli and infiltration with polymorphonuclear leukocytes, there was congestion at the periphery. The convoluted tubules, for the most part, were separated by the increased

interstitial tissue and were atrophic, with noncharacteristic epithelial lining. There were only occasional islands of normal tubules. The lumen contained albumin, many desquamated epithelial cells and in the vicinity of infarcts polymorphonuclear leukocytes. Henle's loops and the secondary convoluted tubules contained fibrin, cellular casts and rarely hyaline cylinders and red blood cells. The epithelial cells of the normal tubules contained fat droplets, occasionally doubly refractile crystals, they frequently showed hyaline droplet degeneration. The majority of the glomeruli were small, with the capillary loops collapsed and bloodless. There were a few fibrosed glomeruli, but more frequently there were all stages of homogenization and fusion of capillary loops, with gradual disappearance of the nuclei. Epithelial proliferation was frequent, with presence of hyaline droplets and fat within these cells. Sporadically, an accumulation of polymorphonuclear leukocytes within the still permeable capillaries was found in the vicinity of the severely damaged loops. Occasionally, necrosis of the tufts was found at the hilus, as well as within the center, extending from the afferent vessel to the capillaries. Here and there were hemorrhagic infarctions of entire glomeruli. Frequent necrosis of the hyalinized vasa afferentia was observed, with extreme narrowing of the lumen or complete closure by small hyaline thrombi without perivascular cell infiltration. The most marked narrowing of the lumen of the interlobular arteries was caused by a cellular intimal proliferation with almost complete obliteration. Sudan stain showed a concentric accumulation of fat in the deeper layers of the intima adjacent to the compressed media and a complete infiltration of the wall of the smallest hyalinized and necrotic vessels with fat. Within the arcuate arteries and proximal portions of the interlobular arteries elastica lamellation was seen, within the smaller branches, only occasional elastica new formation. Of the other organs, only the spleen, pancreas and suprarenal capsule showed moderate hyalinization of the arterioles. The choroid showed extreme intimal proliferation of the small arteries and marked hyalinization and fatty changes of the arterioles.

Diagnosis—The diagnosis was malignant nephrosclerosis, hypertrophy of the heart, particularly of the left ventricle, acute hemorrhagic enterocolitis with ulcerative proctitis, and atherosclerosis of the descending aorta and coronary arteries.

CASE 4—History—A G, a white man, aged 29 engaged in the clothing business, was admitted to Mount Sinai Hospital on Dec 9, 1928. The history was irrelevant. The patient had not had scarlet fever or rheumatic fever. He gave no history of having had venereal diseases. He had always been well, except for occasional sore throats and colds. A few weeks before admission, he noticed frequency of urination during the night. He consulted a physician, who found an elevation of the blood pressure. At the same time, he suffered from suboccipital and frontal headaches. He lost appetite and became weak, and for the last few days before admission he was in bed. During the latter period, he had vomited once, but was not drowsy. Occasional twitchings of the muscles of the legs occurred. For these reasons he was admitted to the hospital.

Examination—The patient impressed one as being chronically ill, he was emaciated and afebrile. The apex of the heart was in the fifth interspace, 10 cm from the midline. The fundi showed intense acute neuroretinitis superimposed on a chronic retinitis. In places the arteries were obliterated, in places thrombosed. The spinal fluid was under increased pressure. On an average of eight readings, the blood pressure was 227 systolic and 139 diastolic.

The urine contained albumin, sediment, hyaline and granular casts and a few red blood cells. The concentration test showed the specific gravity of the urine

fixed at 1 008 The urea nitrogen of the blood, on an average of five examinations, was 29 mg, the uric acid, 3 mg and the creatinine, 3.6 mg The Wassermann reaction was negative On an average of three examinations, the hemoglobin was 50 per cent The red blood cells numbered 3,620,000 and 3,020,000, the white blood cells, 8,800, with polymorphonuclear leukocytes, 40 per cent, lymphocytes, 56 per cent, mononuclears, 3 per cent, and eosinophils, 1 per cent

Course—The patient continued to have severe headaches and vomited profusely He contracted pneumonia and died in pulmonary edema on Dec 27, 1928

Necropsy—Postmortem examination was made by Dr Otonari the next day The heart weighed 520 Gm The right kidney weighed 120 Gm, the left, 100 Gm There were diffuse irregular, flat granulations of the surface The color was brownish red, and there were many pinpoint-sized hemorrhages The cortical markings were indistinct, owing to diffuse grayish streaks and points and occasional hemorrhages

Microscopically, the kidneys showed marked increase in the stroma, numerous small anemic infarcts, interstitial infiltration with lymphocytes and leukocytes and congestion The convoluted tubules were partly arranged in larger islands, a greater part, however, were separated by the stroma proliferation and were often atrophic There were foci of conspicuous dilatation There was fatty and hyaline droplet degeneration of the epithelium The lumen contained cellular debris, occasionally blood, and within Henle's loops occasional calcium casts The majority of the malpighian corpuscles were conspicuously small, their capillaries empty and collapsed Only a few completely hyalinized glomeruli were found, more frequently they showed various phases of developing fibrosis Occasional advanced fatty changes and necrosis of capillaries were noted, with accumulation of leukocytes within adjacent loops Occasional epithelial proliferation with fatty and hyaline droplet degeneration was observed There occurred extreme fatty metamorphosis of arterioles with occasional hemorrhagic infiltration of the wall and nuclear disintegration There was no perivascular cell infiltration Also the interlobular arteries showed severe intimal degeneration with occasional necrosis and thrombosis, as well as extreme narrowing of their lumen by cellular intimal proliferation with fine fat droplets within the external layers, but no inflammatory cells Distinct elastic hyperplastic thickening of the intima of the "arcuate arteries" was seen, and insignificant elastic lamellation farther distally

Of other parts of the body, the spleen, pancreas, prostate, suprarenal glands and intestine showed moderate hyalinization of the arterioles

Diagnosis—The diagnosis was malignant nephrosclerosis, hypertrophy of the left ventricle, atherosclerosis of the descending aorta and peripheral arteries, bronchopneumonia (left lower lobe), chronic calcified tuberculosis of the right upper lobe, tracheobronchial lymph nodes, spleen and liver, right pleural adhesions

CASE 5—History—D. S. J., a white man, aged 41, a worker in a garage, married, was admitted to Mount Sinai Hospital on March 12, 1928 The family history was of no importance In childhood the patient had not had scarlet fever, rheumatic fever or any other diseases He said that he had not contracted any venereal diseases, but his wife had had one miscarriage and two of their children were dead, the third was living and well Ten years before admission, the patient began to have headaches, mainly in the back of the head, they were intermittent Six years before, high blood pressure was detected, the patient had his teeth extracted and adopted a meat-free diet Later his headaches became severe

There was cloudiness of vision for four months. At the time of examination, he was unable to distinguish faces clearly.

Examination—On admission, the patient was irrational, with twitchings of the hands, chronically ill and afebrile. The heart was enlarged. On an average of six readings, the blood pressure was 200 systolic and 148 diastolic, the pressure going down from 238 systolic and 180 diastolic to 144 systolic and 106 diastolic in the last days. The fundi showed neuroretinitis with hemorrhage.

Examination of the urine showed oliguria, albumin + + +, and in the sediment hyaline and granular casts. A concentration test showed the specific gravity to be from 1.010 to 1.020. The urea nitrogen of the blood was from 40 to 71 mg., the uric acid, from 4.6 to 6 mg., and the cholesterol, from 280 to 346 mg., per hundred cubic centimeters. The Wassermann reaction was negative. The blood count showed white blood cells, 10,000, with polymorphonuclear leukocytes, 85 per cent, lymphocytes, 8 per cent, mononuclears, 4 per cent, and eosinophil leukocytes, 3 per cent.

Course—The patient became psychotic, contracted bronchopneumonia and died on March 19, one week after admission.

Necropsy—Necropsy was performed eight hours later by Dr. Otani. The kidneys weighed 170 Gm. each and measured 10 by 5 by 3 cm. They were identical in appearance with those described in the previous cases. Numerous hemorrhages were presented.

Microscopic examination revealed only moderate focal increase in the stroma. The capillaries were congested. There was edema of the interstitial tissue. Fine fat droplets with a few doubly refractile bodies were noticeable within the interstitium. The tubules were generally well preserved and closely arranged, except within the areas of fibrosis. There was much fat and hyaline droplet degeneration. The glomeruli were anemic, very few were hyalinized. Frequent epithelial proliferation and severe degeneration were noted. Fatty changes and necrosis of capillary loops were present. Severe fatty metamorphosis of arteriolar walls was observed, with necrobiosis and hemorrhagic infiltration. There were no inflammatory cells around. There was extreme narrowing of interlobular arteries by cellular intimal proliferation with much fat. Moderate elastica lamellation occurred within the proximal portions of the interlobular arteries (figs. 4 and 5).

Examination of the vessels in other organs showed hyalinization of arterioles in the spleen and the pancreas, changes in two arteries of the testis similar in intensity to those found in the interlobular arteries, but with distinct elastica lamellation, advanced atherosclerosis of branches of the coronary arteries, and extreme intimal proliferation of the small arteries and hyalinization of the arterioles of the choroid. The retina showed many hemorrhages and areas of severe degeneration.

Diagnosis—The diagnosis was malignant nephrosclerosis, concentric hypertrophy of the heart, especially of the left ventricle, atherosclerosis of the aorta and of the coronary and cerebral arteries, hemorrhagic tracheitis and bronchitis, and bilateral bronchopneumonia of the lower lobes.

CASE 6—History—L. G., a white woman, 42 years of age, married, a housewife, was admitted to Mount Sinai Hospital on March 8, 1928. The mother died of high blood pressure, the father, of heart trouble. The patient stated that she had not had scarlet fever, diphtheria, rheumatic fever, venereal disease or any other illness. She had had one miscarriage and one stillbirth. Six months before admission, she had nosebleed, she was told that she had high blood pressure and

kidney disease. For several months she had swollen ankles, breathlessness with palpitation on exertion, and had seen spots before the eyes. These symptoms became severe within the last few days before her admission to the hospital.

Examination—The patient was pale, with puffy eyelids, slightly dyspneic and afebrile. She had fine twitchings of the hands and fingers, slight exophthalmos and a subicteric tint of the sclerae. The thyroid gland was not felt. The heart was markedly enlarged. There was slight edema of the lower extremities. She was disoriented. The fundi showed neuroretinitis and atherosclerosis. On an average of three readings, the blood pressure was 190 systolic and 110 diastolic.

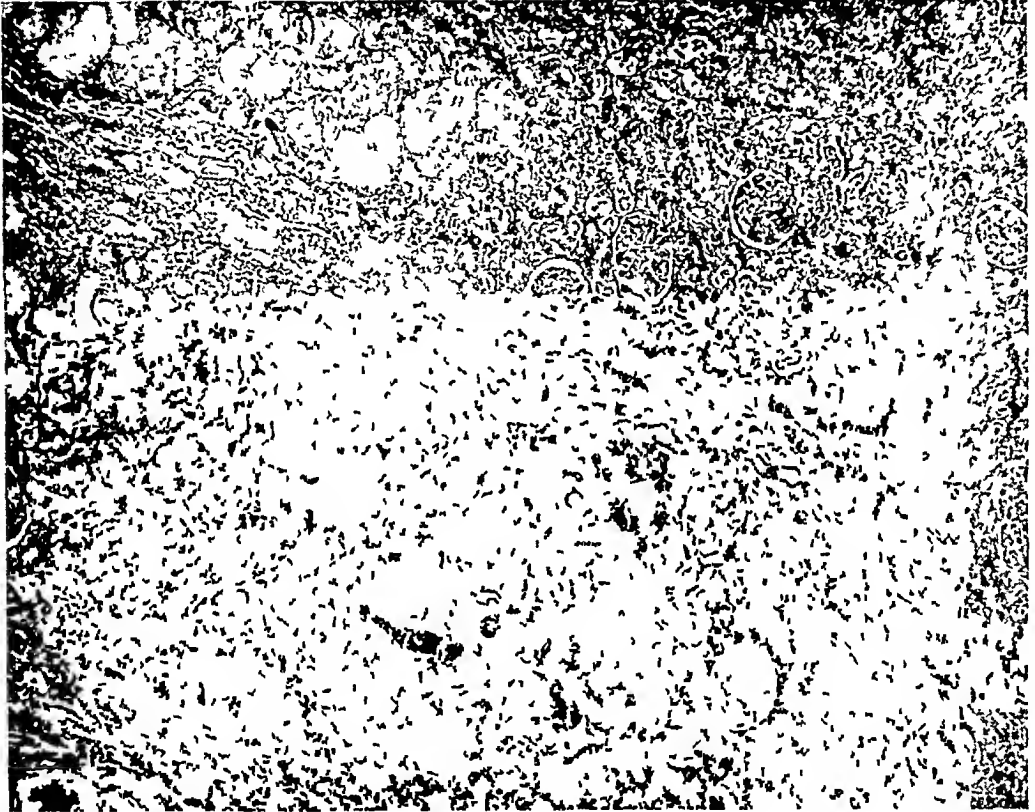


Fig 4 (case 5)—Section showing the very moderate increase in the stroma, the absence of conspicuous tubular alteration or glomerular hyalinization, the anemic glomeruli with collapsed capillaries, the extreme constriction of the interlobular arteries and the severe hyaline and fatty change of the arterioles.

The amount of the urine could not be ascertained because of incontinence. The albumin was +++, the sediment contained granular casts, the specific gravity was 1.006. The urea nitrogen of the blood was from 82 to 112 mg., the uric acid, from 63 to 75 mg., and the creatinine, from 4.4 to 9.5 mg., per hundred cubic centimeters. The Wassermann reaction was twice negative. The blood count gave hemoglobin, 50 per cent, and white blood cells, 10,000, with polymorphonuclear leukocytes, 81 per cent, lymphocytes, 14 per cent, and mononuclear cells, 5 per cent.

Course—The patient went rapidly downhill, and died on March 16, eight days after admission.

Necropsy—Two hours later, postmortem examination was made by Dr Otani. The kidneys weighed 110 Gm each. They were of the same granular appearance as that described in the previous cases. The surface was sprinkled with numerous hemorrhages (fig 6), which appeared also in the cross-section.

Microscopic examination showed the stroma of the kidneys to be increased almost throughout. There were few areas where the tubules were closely packed, generally a loose connective tissue separated them. It was densely infiltrated by lymphocytes mingled with occasional plasma cells and polymorphonuclear leukocytes. The capillaries were congested. In numerous places there was extensive hemorrhage, the origin of which could be traced only in complete serial sections.

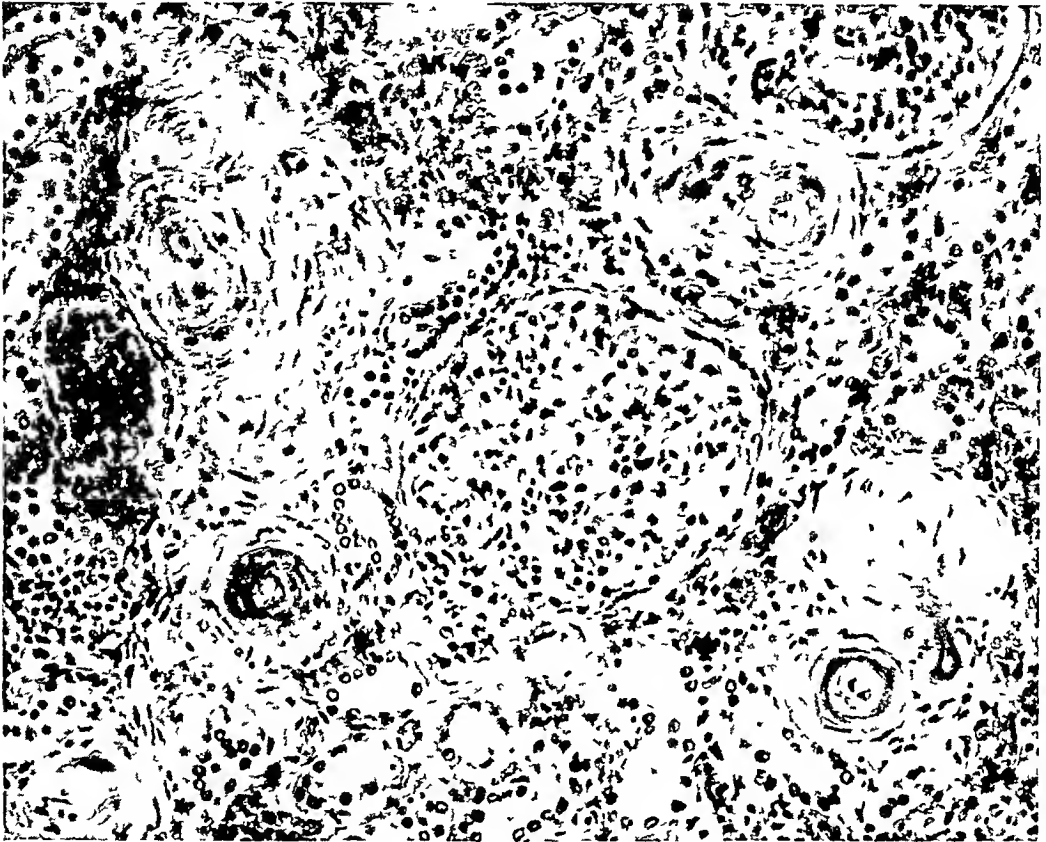


Fig 5—Higher magnification of the upper central part of the same section

The hemorrhages were due to rhexis of small necrotic arterioles, as well as to diapedesis from capillaries that apparently were overfilled because of retrograde passage of blood into the areas where the arterioles had become thrombosed. The glomeruli showed pictures similar to those described in the preceding cases, with the exception that in a great number the capillaries did not present collapsed tufts but well filled, even congested loops. In such instances, serial sections showed the vas afferens to be obliterated by a cellular proliferation in one part of its course (fig 7). The atherosclerotic nature of this closure was suggested because the small vessel originated directly from a large interlobular artery with unquestionable atherosclerosis and in a place where a large atherosclerotic plaque was situated. Since no blood could pass through the arterioles, the congestion of the capillaries could have been the result only of retrograde passage of blood.

The pancreas and spleen showed advanced atherosclerosis, the pancreas to a severe, and the spleen to a moderate, extent arteriolar hyalinization

Diagnosis—The diagnosis was malignant nephrosclerosis, concentric hypertrophy of the left ventricle, dilatation of the right ventricle and auricle, atherosclerosis of the aorta and peripheral arteries, chronic emphysema of the lungs and anasarca

CASE 7—History—M S, a white woman, aged 54, single, was admitted to Mount Sinai Hospital on Aug 13, 1928. The family history was irrelevant. At the age of 18, the patient was sent to Saranac Lake, N. Y., because she had bronchitis. Thirteen years before admission to the hospital, she was told that

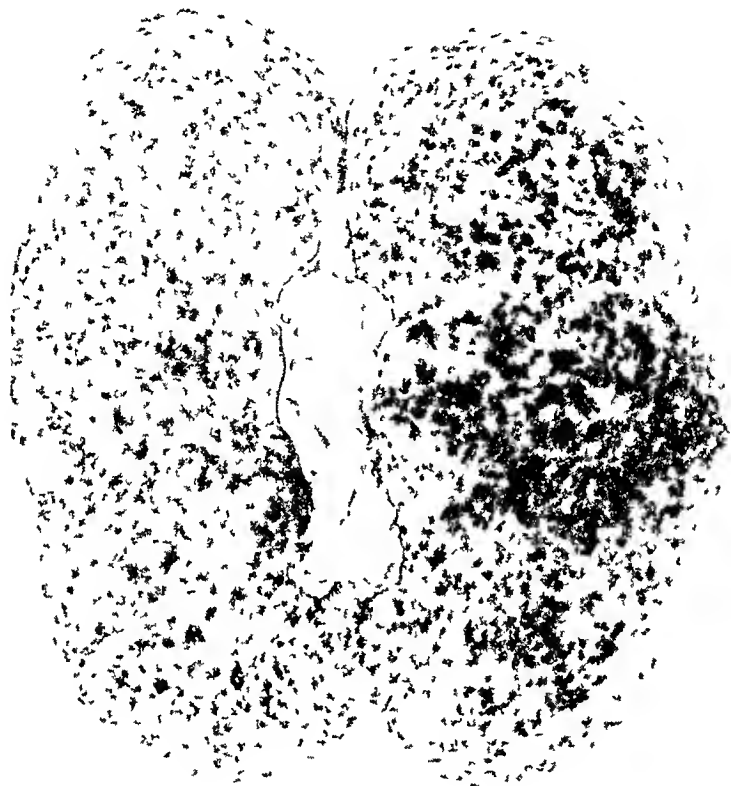


Fig 6 (case 6) —Extensive hemorrhages on the surface

nephrectomy was indicated, but it was not done. Five weeks prior to admission, she entered another hospital, where a diagnosis of chronic nephritis was made. Then for a few weeks she was in a convalescent home. Three days before admission, she became disoriented and delirious.

Examination—The patient had a urinous odor of the breath. She was afebrile. She had occasional twitchings of the muscles of both upper and lower extremities. She had large hemorrhages in the skin of both legs. The fundi presented active neuroretinitis. The chest showed a flattening of the right upper side, dullness in the right upper lobes and a sinus just to the left of the ensiform cartilage, from which oozed greenish-white pus. Roentgen examination revealed tuberculous osteomyelitis of the second and seventh ribs. The heart was markedly enlarged. There were a bilateral Kernig sign, marked rigidity of the neck and a permanent

Babinski reflex in the toes. The spinal fluid was under pressure. The blood pressure was 165 systolic and 110 diastolic.

The urine contained albumin (++), many granular casts and white blood cells. The specific gravity was 1.020. The urea nitrogen of the blood was 43 mg per hundred cubic centimeters.

Course—The spinal fluid at the time of death contained 400 white blood cells, 80 per cent of which were polymorphonuclear leukocytes. Bacteriologic examination yielded negative results, and inoculation of a guinea-pig was unsuccessful because the animal died too early.

The clinical diagnosis was tuberculous meningitis and chronic glomerulonephritis with azotemia.

The patient died two and one-half days after admission.

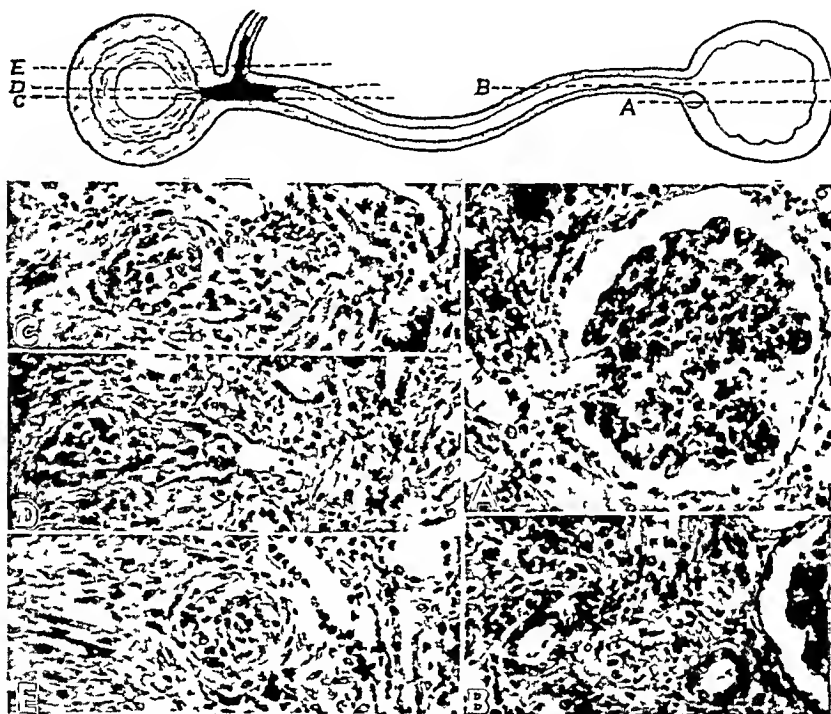


Fig 7 (case 6)—A serial section reconstruction of a glomerulus and vas afferens. *A*, engorged capillaries and vas efferens, *B*, vas afferens (distal portion) patent, *C* and *D*, vas afferens (proximal portion where it branches off the interlobular artery) completely obliterated by cellular intimal proliferation, and *E* cross-section of another obliterated arteriole. Note the reticulated arrangement of the cells.

Necropsy—Necropsy was performed seven hours after the patient's death by Dr Klemperer. Permission to open the head was not obtained. The right kidney weighed 120 Gm and measured 10 by 5 by 3 cm. It had the same appearance as the kidneys in the other cases. The left kidney had a very narrow cortex due to compression caused by the tuberculous pyonephrosis.

Microscopically, the changes were almost identical with those in the other cases. The stroma increase was slighter. An extreme narrowing of the interlobular arteries leading to complete closure was observed with a proliferation of

the intima showing more fibrillar differentiation and distinct elastica lamellation within the outer zone

Marked hyalinization of the arterioles was found in the spleen and pancreas, moderate hyalinization, in the liver and suprarenals

Diagnosis—The diagnosis was malignant nephrosclerosis, chronic tuberculous pyonephrosis of the left kidney with inspissation, concentric hypertrophy of the ventricle, hypertrophy and dilatation of the right ventricle, tuberculous osteomyelitis of the second right and seventh left rib, and multiple pleural adhesions

CASE 8—History—L. R., a white man, 23 years of age, single, an embroiderer, was admitted to Mount Sinai Hospital on Feb 16, 1926. The family history was irrelevant. The patient had scarlet fever at the age of 2, he had had no rheumatism or other acute infections. Tonsillectomy had been performed on him one year before because of frequent tonsillitis. For about five years he had had occasional severe bitemporal headaches, which gradually became worse. About one year before, he was told that he had high blood pressure. Eight weeks before, his vision became blurred. Two or three weeks before, he began to vomit, this condition had become worse within the last few days before admission. He had oliguria.

Examination—On admission, the patient was drowsy and afebrile. His heart was enlarged to the left. On an average of four examinations, the blood pressure was 235 systolic and 150 diastolic. It fell to 168 systolic and 100 diastolic shortly before death. The fundi showed an advanced albuminuric retinitis. The urine decreased in amount.

Examination of the urine showed albumin + + +, the sediment showed occasional red blood cells and many leukocytes. The urea nitrogen of the blood was 63 mg, the creatinine, 8 mg, and the uric acid, 11 mg, per hundred cubic centimeters. The Wassermann reaction was negative. The blood count showed hemoglobin, 70 per cent, red blood cells, 3,340,000, and white blood cells, 17,000, with polymorphonuclear leukocytes 83 per cent, lymphocytes 15 per cent, and mononuclear cells, 2 per cent.

Course—The patient became comatose forty-eight hours before death and died on February 24, eight days after admission.

Necropsy—Necropsy was performed eighteen hours later by Dr. Gross. The left kidney weighed 105 Gm, and the right, 120 Gm. Each measured 11 by 5 by 3 cm. The surfaces were slightly granular. Many hemorrhages were seen.

Microscopic examination showed insignificant, only focal increase in the stroma. Occasional small anemic infarcts were seen, with leukocytic infiltrations. There was marked dilatation of the convoluted tubules, which contained occasional polymorphonuclear leukocytes. Only a few fibrosed glomeruli were observed. The majority were bloodless, with collapsed capillaries, some, however, were engorged, almost infarcted. They presented slight proliferative and degenerative epithelial changes. There was marked necrosis of arterioles, with hemorrhagic penetration of the wall and often thrombotic occlusion. The vasa afferentia were focally extremely narrow, in some parts of the cortex, however, they were not altered. The interlobular arteries were extremely narrowed by cellular intimal proliferation.

The arterioles of the spleen, pancreas and suprarenals showed hyalinization.

Diagnosis—The diagnosis was malignant nephrosclerosis, hypertrophy of the left ventricle, acute fibrinous pericarditis, and hemorrhagic focal pneumonia of the left lung.

CASE 9—*History*—H P, a white woman, 26 years of age, married, a housewife, was admitted to Mount Sinai Hospital on Nov 7, 1925. The father died of kidney trouble. The patient had measles in childhood. Seven years before admission, she had typhoid fever. Two years before, a tonsillectomy was performed on her. Occasionally she had severe headaches. For one and one-half years, the headaches had become worse and more frequent, which prevented her from working. For one year, she had had attacks of substernal pain, and for seven months, nocturia. For two weeks, she had suffered from uncontrollable vomiting. Within the last thirty-five hours before admission she was anuric.

Examination—When admitted, she was afebrile and restless, tossing about and complaining of extreme weakness. The breath was urinous. The heart was markedly enlarged. The blood pressure in an average of eleven readings was 230 systolic and 145 diastolic. The fundi showed neuroretinitis. Very small amounts of urine were passed. Concentration was from 1 006 to 1 012. The result of the test for albumin was ++. The sediment contained a few granular casts, white blood cells and an occasional red blood cell. The blood showed urea nitrogen, from 81 to 102 mg, uric acid, 8.5 mg, and creatinine, 14 mg, per hundred cubic centimeters. The blood count gave hemoglobin, 60 per cent, red blood cells, 3,320,000, and white blood cells, 8,200.

Course—Fluids were forced, which caused a drop in the urea nitrogen of the blood, but edema and ascites developed. The patient died of uremia on November 19, twelve days after admission.

Necropsy—On the day after death, Dr. Romanoff made a postmortem examination. The right kidney weighed 120 Gm and measured 11 by 6 by 3 cm. The left weighed 40 Gm and showed only three pyramids. They showed slightly granular surfaces and many hemorrhages.

Microscopically, the kidneys presented a diffuse increase in the stroma and many hemorrhages. The same glomerular changes were seen as in the other cases. There was severe arteriolar necrosis without a perivascular inflammatory reaction. Portions of the interlobular arteries were markedly narrowed by dense intimal proliferation.

The arterioles of the spleen and pancreas showed hyalinization.

Diagnosis—The diagnosis was malignant nephrosclerosis, hypertrophy of the left ventricle, acute fibrinous pericarditis, and hypoplasia of the left kidney, with anomalous implantation of the ureter.

CASE 10—*History*—T P, a colored woman, 57 years of age, married, a housewife, was admitted to the hospital on July 19, 1927. The patient's family history was irrelevant. Nine years before she had influenza. Six children were living and well, one child had died. The menopause occurred five years before. The patient had never been sick. Three weeks before, she became ill with general malaise, vomiting and incontinence. Then she became restless, and she said that she felt a lump behind the sternum. She became disoriented and psychotic.

Examination—She was admitted to the hospital in stupor, but could be aroused with difficulty. The temperature was normal. The heart was slightly enlarged. The blood pressure was 165 systolic and 110 diastolic. The fundi showed albuminuric retinitis and optic neuritis.

Only 30 cc of urine was passed in the previous twenty-four hours. The concentration was 1 005. Albumin was ++, the sediment contained many granular and hyaline casts and white blood cells. The blood showed 186 mg of urea nitrogen per hundred cubic centimeters. The Wassermann reaction was negative.

Course—The patient died on July 20, twenty-four hours after admission

Necropsy—Necropsy by Dr Klemperer, fifteen hours later, showed the kidneys to be smaller than normal (weight omitted), measuring 9 by 5 by 2 cm, with diffuse slightly elevated granulations and numerous hemorrhages

Microscopic examination revealed a diffuse increase in stroma, with atrophy of the tubules, small glomeruli, often bloodless, with collapsed capillaries, few hyalinized glomeruli, occasional malpighian corpuscles with hemorrhagic infarction and necrosis of the tufts, frequent arteriolonecrosis without perivascular inflammation, and marked narrowing of the interlobular arteries by a dense, fibrillar connective tissue, with coarse elastic lamellation in the outer zone and occasional fine elastic fibers in the inner layer

The arterioles of the liver, spleen and pancreas showed moderate hyalinization

Diagnosis—The diagnosis was malignant nephrosclerosis, cerebral atherosclerosis, small acute ulcer of the stomach, hypertrophy of the left ventricle, and a small endothelioma of the dura

CASE 11—History—T L, a white woman, aged 46, married, a housewife, was admitted to the hospital on Sept 5, 1928. The patient's father died at the age of 72, the mother died as a young woman, the cause of death being unknown. One sister had kidney trouble. The patient gave no history of having had scarlet fever, rheumatic fever or diphtheria. Nineteen years before, she had an abscess of the breast. She had occasional colds. Six children were living and well, there had been three miscarriages. For three years the patient had suffered from severe suboccipital headaches in the morning. For three years she had had nocturia, also frequency of urination during the day. There was occasional incontinence at night. She noted precordial pressure and palpitation. All symptoms grew worse, especially during the three weeks before admission.

Examination—When admitted, the patient complained of severe precordial constriction, a few minutes later she had a severe attack of dyspnea and a sensation of impending death. She was afebrile. Her breath was uriferous. There was enlargement of the heart. The blood pressure, in an average of seven readings, was 210 systolic and 135 diastolic. The fundi showed acute neurorhinitis on an old atherosclerotic basis.

The urine was small in amount, the albumin was ++, the sediment contained many white blood cells, a few red blood cells and rare granular casts, the concentration was from 1010 to 1012, the phenolsulphonphthalein excretion was 0 after four hours. The blood showed urea nitrogen, from 93 to 108 mg, uric acid, 51 mg, and creatinine, from 97 to 124 mg, per hundred cubic centimeters. The Wassermann reaction was negative. The hemoglobin was 74 per cent at admission, it fell to 46 per cent before death. The red blood cells numbered 4,600,000, the white blood cells, 11,400.

Course—Pulmonary edema and cardiac failure developed, and the patient died on September 28, three weeks after admission.

Necropsy—Two hours later, Dr Otani made a postmortem examination. The kidneys weighed 85 Gm each, their size was 10 by 5 by 3.5 cm. They showed diffuse prominent grayish-yellow granulation and a few punctate hemorrhages. There was marked atherosclerosis of the renal artery (fig 8).

Microscopic examination revealed a diffuse marked increase in the stroma, with separated islands of normal tubular parenchyma. The glomeruli were not extensively fibrosed, but were mostly small and anemic, with collapsed capillaries (fig 9). There was moderate arteriolonecrosis, but severe intimal proliferation of the interlobular arteries with excessive narrowing of the lumen. There was

elastica lamellation in the outer layer and cellular proliferation of connective tissue in the inner layer, which showed fatty infiltration and focal necrobiosis, with impregnation of the wall by erythrocytes (fig 10 A)

The spleen was very firm. The surface was nodular. The large nodes were separated by firm, depressed, scarlike areas. On section, the pulp was purplish red. The trabeculae were prominent. Several irregular, firm and dry yellowish-white areas of necrosis interrupted the otherwise dark red cut surface, giving the spleen a mosaic-like appearance.

Microscopic examination showed within the deeply congested pulp several necrotic areas of irregular outline. The intratrabecular arteries and their branches showed extreme narrowing due to a cellular intimal proliferation in the outer



Fig 8 (case 11) —The more advanced type of renal atrophy with prominent granulation. Note the few hemorrhages on the surface, the narrow cortex on cross-section and the severe atherosclerosis of renal artery.

coat of which there was distinct coarse elastica lamellation (fig 10 B). The narrow lumen was occasionally obliterated by hyaline thrombi.

The pancreatic arteries of the same size as the interlobular renal arteries showed extreme narrowing due to the same cellular intimal proliferation (fig 10 C and D).

Diagnosis—The diagnosis was malignant nephrosclerosis, hypertrophy and dilatation of both ventricles and auricles, chronic passive congestion of the lungs, liver and spleen, brown induration of the lungs, generalized atherosclerosis, hydrothorax, ascites, and multiple necrosis of the spleen.

CASE 12—History—T. S., a white woman, aged 55, a housewife, was admitted to the hospital on Oct. 1, 1927. The family history was irrelevant. The previous

history was unimportant. The menopause occurred when she was 45 years old. About twenty years before admission to the hospital, the patient was told that she had hypertension. For ten years she had had increasing dyspnea on moderate exertion. Slight nocturia had developed in the past five years. She was admitted to the hospital because of hypertension and persistent vomiting for weeks.

Examination—The patient was lethargic and afebrile and had a urinous breath. The heart was markedly enlarged. The fundi showed neuroretinitis. The blood pressure was 234 systolic and 110 diastolic.

The amounts of urine were small. The albumin was ++, the sediment contained a few coarse granular casts and many white and red blood cells. The

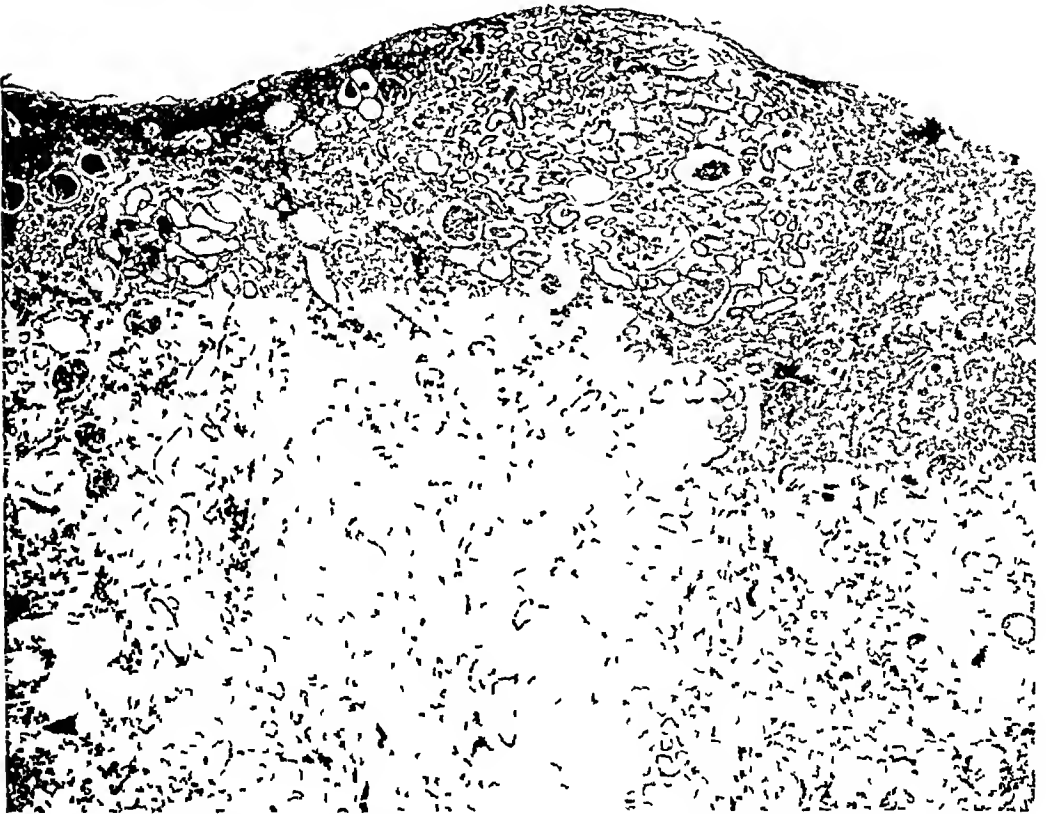


Fig 9 (case 11) —The advanced increase in the stroma and the atrophy of the parenchyma. Compare this with figure 4.

concentration was from 1007 to 1010. The blood disclosed urea nitrogen, 121 mg, uric acid, 54 mg, and cholesterol, 218 mg, per hundred cubic centimeters. The Wassermann reaction was negative. The blood count gave hemoglobin, 70 per cent, and white blood cells, 11,200, with polymorphonuclear leukocytes, 84 per cent, and lymphocytes, 16 per cent.

Course—The patient became stuporous. Muscular twitchings developed. Death occurred on Oct 7, 1927, six days after admission.

Necropsy—Five hours later, Dr. Otani made a postmortem examination. The left kidney weighed 110 Gm, the right, 120 Gm. The surfaces were finely granular throughout. The cortex was narrow, the cortical markings were obscured by a grayish-white infiltration.

Microscopic examination revealed diffuse marked increase in the stroma, but many islands of dilated, otherwise normal tubules. The tubules elsewhere were separated and often atrophic. The glomeruli were not extensively fibrosed, but were generally anemic or bloodless, except for a few that showed hemorrhagic infarction. Occasional epithelial proliferation was seen. Necrosis of the tufts was rare. Arteriolonecrosis without perivascular infiltration was present. There was excessive narrowing of interlobular arteries, with distinct elastica lamellation in the outer coats of the intima.

The arterioles of the pancreas, liver, spleen and suprarenals showed marked hyalinization of the arterioles and atherosclerotic narrowing of the small arteries.

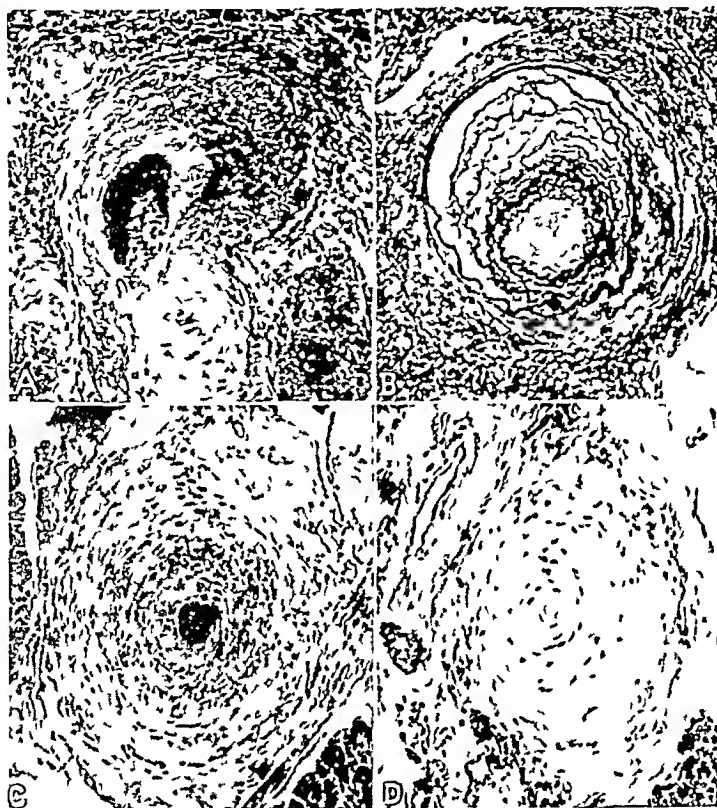


Fig 10 (case 11) —*A*, an interlobular artery of the kidney showing intimal proliferation and focal necrobiosis and aneurysmic dilatation. The wall and the perivascular stroma are impregnated with erythrocytes and hemoglobin droplets. *B*, splenic artery of the same caliber as that shown in *A* found near necrosis, showing closure of lumen by a similar intimal proliferation. Note the conspicuous elastica lamellation and the numerous foam cells as evidence of the degenerative nature of the process. *C* and *D*, identical arterial changes in the pancreas. Note the hemorrhagic impregnation of the wall in *C*.

Diagnosis—The diagnosis was malignant nephrosclerosis, hypertrophy of the left ventricle, atherosclerosis of the aorta, coronary arteries and pulmonary artery, chronic passive congestion of the liver, lungs and spleen, ascites, and calcified tuberculosis of the left lung and tracheobronchial lymph nodes.

CASE 13—History—H. O'N., a colored man, married, aged 53, a waiter, was admitted to the hospital on Jan 16, 1929. The family history was irrelevant.

The patient was a user of alcohol. Twelve years before, the patient had rheumatism. Two and one-half months before, a stone in the bladder was removed by crushing. For two and one-half months, the patient had suffered from frontal headaches in the morning. Two weeks before admission, he suddenly became seriously sick, began to vomit and became drowsy and lethargic.

Examination—When admitted, he was afebrile and cachectic and had a urinous odor to his breath. He showed occasional muscular twitchings. The heart was enlarged. The fundi showed neuroretinitis, atherosclerosis and atrophy of the optic nerve. The blood pressure was 180 systolic and 100 diastolic.

The output of urine was smaller than the intake of fluid. The concentration was 1010, the result of the test for albumin was ++, the sediment contained a few white and red blood cells. The blood showed urea nitrogen, 190 mg, uric acid, 15 mg, and creatinine, 16 mg, per hundred cubic centimeters. The Wassermann reaction was ++++. The blood count showed hemoglobin, 39 per cent, and white blood cells, 15,200, with polymorphonuclear leukocytes, 84 per cent, lymphocytes, 14 per cent, and mononuclears, 2 per cent.

Course—The patient died on January 18, two days after admission. Urea crystals had developed on his face and neck.

Necropsy—Two hours later, Dr Klemperer performed an autopsy. The right kidney weighed 95 Gm, the left, 140 Gm. Both showed diffuse flat granulations. The right kidney showed a deep scar penetrating the cortex in its middle third, apparently a circumscribed atrophy caused by a calculus. Numerous hemorrhages were evident on the surface and section and within the pelvis.

Microscopic examination showed a moderate but diffuse increase in the stroma, with separation and frequent atrophy of the tubules. Only a few hyalinized glomeruli were seen, generally they were small and anemic and occasionally they showed epithelial proliferation, fatty and hyaline droplet degeneration and necrosis of loops. Arteriolonecrosis was present, but was not severe. There were no perivascular infiltrations. Excessive narrowing of the interlobular arteries by a cellular intimal proliferation was seen. Elastic lamellation was present in the larger branches.

The arterioles of the spleen, liver, pancreas and stomach showed marked hyalinization. Within the intestines, only moderate arteriosclerosis was seen. The small arteries showed moderate atherosclerosis, except in the pancreas, where arteries of the caliber of the interlobular renal arteries were found with extreme cellular intimal thickening. In their vicinity, small areas of necrosis of the parenchyma were encountered.

Diagnosis—The diagnosis was malignant nephrosclerosis, hypertrophy and dilatation of the left ventricle, atherosclerosis of the aorta and peripheral blood vessels, uremic ulcers of the large intestine, and circumscribed cicatricial atrophy of the right kidney (stone).

CASE 14—History—M. B., a white woman, 39 years of age, married, a telephone operator, was admitted to the hospital on March 26, 1929. The family history was irrelevant. In childhood, the patient had diphtheria, scarlet fever and measles. At the age of 18 years, she had a left mastoidectomy. She had suffered two miscarriages. She had had an appendectomy and an oophorectomy. During the last year, she had lost 80 pounds (36.3 Kg). Four months before admission, she was hit on the eye by a baseball. She went to the neurologic institute because of nervousness and defective vision. She was admitted to Mount Sinai Hospital because of sudden loss of speech and difficulty in swallowing.

Examination—When admitted, she was afebrile and aphasic, with a partial motor aphasia and right central facial paresis. The deep reflexes on the left side were exaggerated. Babinski's sign was noted on the left side. The clinical diagnosis was focal cerebral lesions of the left hemisphere. The fundi showed neuroretinitis. The heart was enlarged. The blood pressure was between 185 systolic and 90 diastolic and 240 systolic and 150 diastolic.

Examination of the urine showed concentration, 1 010, albumin, + + +, and a few red and white blood cells in the sediment. The blood showed urea nitrogen, from 45 to 57 mg, uric acid, 8 mg, and creatinine, 6.2 mg, per hundred cubic centimeters. The blood count gave hemoglobin, 35 per cent, red blood cells, 1,250,000, and white blood cells, 11,800, with polymorphonuclear leukocytes, 86 per cent.

Course—The patient began to have difficulty in respiration and later pericarditis, and died on April 8, twelve days after admission.

Necropsy—Eight hours later, a postmortem examination was made by Dr. Otani. Permission to examine the brain was not obtained. The kidneys weighed 120 and 110 Gm. They showed diffuse flat granulations and numerous hemorrhages. There was severe atherosclerosis of the renal artery.

Microscopic examination revealed a diffuse increase in the stroma but not extensive scar formation. The structure of the cortex was not completely obscured. The tubules were separated and often atrophic. Few fibrosed glomeruli were encountered. Many glomeruli were small and anemic, with collapsed tufts. Some showed partial hyalinization. Occasional epithelial proliferation and fatty hyaline droplet degeneration of the proliferated and desquamated cells were seen. Occasional necrosis of the capillaries was seen. Arteriolonecrosis without perivascular infiltration and extreme intimal proliferation of the interlobular arteries were features.

The arterioles of the spleen, suprarenals and pancreas showed severe hyalinization, which was less marked in the liver, intestine and esophagus. There was severe atherosclerosis of branches of the coronary arteries.

Diagnosis—The diagnosis was malignant nephrosclerosis, hypertrophy of the left ventricle, atherosclerosis of the aorta and coronary arteries, acute fibrinous pericarditis, bronchopneumonia of the right lower lobe, fatty degeneration and fibrosis of the myocardium, and multiple calculi of the pancreatic duct, with fibrosis of the body.

CASE 15—History—S. G., a white man, aged 36, a laborer, was admitted to the hospital on Aug. 9, 1929. The family history was irrelevant. The previous history was unimportant. Two years before admission, the patient had frontal headaches and occasional epistaxis. He was informed that he had high blood pressure. He stopped work and improved under rest. Three months before, the frontal headaches reappeared. He had nocturia (three or four times). Palpitation and precordial pains were experienced on exertion. Dimness of vision had been present for four weeks. For three days there had been nausea and vomiting.

Examination—Physical examination showed a very sick anemic person with a urinous odor of the breath and no elevation of temperature. He was dyspneic and orthopneic at rest. The heart was markedly enlarged. The fundi disclosed hypertensive neuroretinitis. The blood pressure, in an average of four readings, was 234 systolic and 143 diastolic.

The urine showed a concentration of from 1 006 to 1 010. There was from a trace to + albumin. The sediment contained casts and white blood cells but no red blood cells. The blood showed urea nitrogen, from 79 to 135 mg, uric acid,

85 mg, and creatinine, 10 mg, per hundred centimeters. The blood count gave hemoglobin, from 42 to 23 per cent, white blood cells, 7,600, and red blood cells, 2,200,000.

Course—The patient went continuously downhill, and died of uremia on August 30, three weeks after admission.

Necropsy—Nineteen hours after death, a postmortem examination was made by Dr. Otani.

The weight of the left kidney was 100 Gm, that of the right, 80 Gm. There were several depressed scars, which had destroyed the entire cortex, and a diffuse flat granulation of the entire surface. The cortical markings were indistinct.

Microscopic examination showed the cortical structure obliterated in many fields by scar tissue within which numerous fibrosed glomeruli were seen. Outside of these areas, however, there was not a marked increase in the stroma. Here the glomeruli were frequently markedly congested, but others were small and collapsed. Arteriolonecrosis was found rarely. The interlobular and arcuate arteries, however, showed an extreme degree of narrowing due to a combination of typical atherosclerosis with elastica lamellation in the outer, and a cellular intimal proliferation in the inner, coats.

Only the arterioles of the liver and spleen showed moderate hyalinization.

Diagnosis—The diagnosis was malignant nephrosclerosis, hypertrophy of the heart, especially of the left ventricle, acute fibrinous pericarditis, atherosclerosis of the aorta and of the pulmonary and coronary arteries, acute enterocolitis, focal pneumonia of the right lower lobe, bilateral hydrothorax, ascites and passive congestion of the liver and spleen.

CASE 16—History—E. L., a white woman, aged 32, single, a dressmaker, was admitted to the hospital on May 28, 1929. The family history was irrelevant. The patient had always been well, except for influenza in 1918. Two years before, she was refused life insurance because of high blood pressure. She felt, however, perfectly well at that time. One year before, she noticed an increasing weakness and easily became fatigued. Six months before her blood pressure was 280. She began to have frequency of urination and developed edema of the ankles and a swelling in the sacral region. Two weeks before admission, she had an attack of complete amaurosis, which disappeared. She was admitted to the hospital because of increasing dyspnea and orthopnea.

Examination—On admission, she was afebrile, but very sick, with a urinous odor of the breath. The heart was enlarged. The fundi showed hemorrhagic neuroretinitis. There was marked edema of the lower extremities. The abdomen was distended, and the liver was enlarged. Scattered about the abdomen were small purpuric hemorrhages. The blood pressure was 242 systolic and 112 diastolic.

The urine showed a specific gravity of from 1.004 to 1.012, albumin, +. The sediment contained white and red blood cells. The blood yielded urea nitrogen, from 87 to 183 mg, uric acid, 14 mg, and creatinine, 16 mg, per hundred cubic centimeters. The blood count gave hemoglobin, 39 per cent, white blood cells, 7,400, and polymorphonuclear leukocytes, 86 per cent. The Wassermann reaction was negative.

Course—The patient became increasingly drowsy. Urea crystals developed on her face. She had numerous twitchings of the extremities and hiccups. She died on June 2, eleven days after admission.

Necropsy—The following day, necropsy was performed by Dr. Otani. The kidneys weighed 85 Gm each. The surfaces were diffusely granular, the granules

were larger than in the other cases. On the surface and on cross-section there were numerous hemorrhages.

Microscopic examination showed a diffuse increase in the stroma, with numerous connective tissue scars alternating with islands of well preserved tubules. The cortical structure was obscured by the presence of many atrophic and dilated tubules. Glomerular fibrosis was more conspicuous on the surface than inside the cortex, but was not extensive. Various phases of the process of atrophy were present. The majority of the malpighian corpuscles were not hyalinized, but were small and anemic, with collapsed, often thickened, capillary loops. Rarely there were necrosis of the tufts and epithelial proliferation. Arteriolar hyalinization was conspicuous. A few necrotic arterioles were seen, without perivascular cell infiltration. There was extreme narrowing of the interlobular arteries by dense intimal proliferation with conspicuous elastica lamellation in the outer zone. However, here and there one found a more cellular intimal proliferation.

Within the body of the pancreas, an area 1.5 cm. in diameter was necrotic and liquefied. A few smaller necrotic foci were also present.

Microscopically, numerous foci of necrosis of the parenchyma were observed, some with organization and some with advanced fibrosis. The arteries of the size of the arcuate arteries of the kidneys and their interlobular ramifications showed an extreme cellular intimal thickening, which often almost occluded the lumen. Occasionally, the lumen was filled with a thrombus, which sometimes showed organization and canalization. The internal elastic lamella sharply separated the media from the intima. The fibroblasts that formed the thickened intima often showed hyaline droplet degeneration and necrobiosis. The walls of such vessels were often impregnated with red blood cells. An inflammatory reaction was seen only in the adventitia and media of vessels lying within or next to necrotic foci. Only one arteriolar cross-section showed necrosis without perivascular infiltration.

Routine examination of the other organs revealed only within the spleen advanced atherosclerosis of the small arteries and hyalinization of the arterioles. The liver and the gallbladder showed only slight changes. The coronary arteries were severely affected by atherosclerosis, but the myocardial branches showed no changes.

Diagnosis—The diagnosis was malignant nephrosclerosis, hypertrophy of both ventricles of the heart, atherosclerosis of the aorta and of the coronary and splenic arteries, focal necrosis of the pancreas, pseudomembranous enteritis (ileum and jejunum), purulent bronchitis and peribronchitis, chronic calcified tuberculosis of both lungs and tracheobronchial lymph nodes, hydrothorax on the right side, and ascites.

SUMMARY OF CASES

Before entering on a detailed discussion and evaluation of our observations, it may be well to summarize the clinical events and the morbid process.

The importance of these cases for clinical medicine and pathology is obvious from table 1, which presents the number and percentage of deaths from the different types of renal disease observed by us within the last three years.

In this survey, almost 30 per cent of all deaths from renal insufficiency were of the type of malignant nephrosclerosis as understood by Fahr. The ages of the patients are tabulated in table 2.

The average age in our cases was 39 years. In agreement with Fahr and other authors, we found that the majority of cases occurred in persons below 50 years, and this is contrasted with the situation in cases of benign sclerosis, in which the majority of the patients were above 50 years.

Cases occurred equally in both sexes. We observed cases in eight females and eight males. The average age of the female patients was 44 years, and that of the male patients was 30 years.

Except in one case, fatal renal insufficiency was preceded by a pure hypertensive phase with symptoms of varying degree. The duration

TABLE 1—*The Number and Percentage of Deaths from Different Types of Renal Insufficiency Observed by the Authors*

	Number of Deaths	Percentage
Acute and subacute glomerular nephritis	8	13.8
Chronic glomerular nephritis	19	32.7
Malignant nephrosclerosis	16 (1)*	29.3
Benign decompensated nephrosclerosis (Fahr)	7	12.0
Amyloid contracted kidney	4	7.0
Polycystic kidney	3	5.2
Total	58	100.0

* See case 18

TABLE 2—*Age of Patients with Malignant or Benign Sclerosis*

Age	Malignant Sclerosis	Benign Sclerosis
0 to 10	1	0
11 to 20	0	0
21 to 30	4	0
31 to 40	3	4
41 to 50	4	14
51 to 60	4	16
61 to 70	0	22
71 to 80	0	6
Total	16	62

of the antecedent hypertension was not easy to determine. In several cases, the hypertension had been discovered accidentally in an examination for life insurance, with the patient apparently in perfect health. In other cases, symptoms had set in so insidiously that it was impossible to say precisely when they had appeared. This antecedent phase did not differ in any way from other hypertensive states. It passed into the terminal uræmic stage abruptly or sometimes after an interval of several months with increased intensity of hypertensive symptoms, such as uncontrollable headaches or occasional cardiac insufficiency, or after a period of failing vision. The exact start of the renal insufficiency was ascertained only when the patients had been under careful medical control for some time before their admission to the hospital, otherwise, it could be only surmised from the clinical symptoms of obstinate nausea

and vomiting, restlessness and psychic disturbance. The temperature was always normal on admission. The chemical examination of the blood, performed in every case immediately after admission, always disclosed a marked increase in the values of urea nitrogen, uric acid and creatinine. The systolic and diastolic blood pressure was much elevated, as a rule the average being 232 systolic and 140 diastolic. In eight cases, during the last days of illness, there were oliguria and even anuria. The specific gravity of the urine was always low, and the concentrating power of the kidneys was lost. Albumin was present regularly, the sediment contained hyaline and granular casts, white blood cells and occasionally blood. Examination of the blood often showed considerable anemia, but leukocytosis only occasionally. The Wassermann reaction was negative, except in one case. In all the other cases, there was neither clinically nor anamnesticly any evidence of previous syphilitic infection. The eyegrounds in all cases, except one in which they were not examined, revealed neuroretinitis. The average duration of the renal insufficiency, so far as it could be determined from the history, was thirty-two days. Especially striking was the rapid course of the illness, which went on without remission and could not be influenced by therapy once the uremic symptoms had appeared.

The gross anatomic picture was characterized by predominant changes in the kidneys and the heart. In thirteen cases there was atherosclerosis of the aorta and peripheral blood vessels. (Unfortunately, permission to examine the brain was secured in three cases only.) Acute fibrinous pericarditis occurred in six cases. Circumscribed anemic necrosis of the pancreas due to severe alteration of the small vessels was observed twice, and once multiple necrosis of the spleen was found. Hemorrhagic enterocolitis with or without ulcerations was present in four cases. Purpuric skin eruptions were encountered in two cases, and urea crystals in two cases. Terminal bronchopneumonia was observed seven times. Hydrothorax, ascites or anasarca existed in five cases. Chronic tuberculous lesions of the lungs were found in four instances. An old tuberculous pyonephrosis was present in one case in which there also existed a tuberculous osteomyelitis of the sternum and two ribs.

The heart was markedly enlarged in every case, except in one in which there was extreme emaciation of the body. The average weight of the heart, including the aorta ascendens, was 550 Gm. The left ventricle was always preponderant, but coexisting hypertrophy of the right ventricle was seen in six cases, in two of which there was gross brown induration of the lungs, indicating relative insufficiency of the left side of the heart. Sclerosis of the coronary arteries moderate in degree, was present in ten cases. One case showed an old thrombotic

occlusion of the ramus posterior descendens of the right coronary vessel and another severe atherosclerosis of the same branch, in both cases there was advanced myocardial fibrosis

The kidneys in the majority of instances were only slightly reduced in size, the average weight being 113 Gm. In one instance, the left kidney was hypoplastic, weighing 40 Gm, and showing only three pyramids. The renal surface was always diffusely granular with flat irregularly sized brown elevations above slightly depressed red areas. A few deeper depressions of the type found in renal atherosclerosis of the decrescent form were observed in eight cases. These diffuse depressed areas gave the organ the predominant brownish-red color which contrasted with the bright petechial hemorrhages, more or less numerous, seen in every case. In one case the surface and the cross-section were densely sprinkled with hemorrhages, ill-defined in outline, and of the size of a pinhead or larger. On cross-section, the cortex and the medulla were for the most part sharply demarcated, the cortical markings, however, were obscured by infiltrating grayish streaks and flecks. The cross-sections of the arcuate vessels were for the most part thickened and gaping. The medulla was generally normal. The pelvis frequently showed deep red hemorrhages. The renal artery was markedly thickened in six cases.

The microscopic changes disclosed a uniformity similar to that noted in the gross lesions. Chief among these changes was the severe vascular damage. The extreme narrowing of the interlobular arteries caused by a cellular intimal proliferation, and the necrosis of the arterioles, were present in every instance. The alteration of the glomeruli, though less conspicuous, consisted in (1) collapse of the capillaries and anemia, (2) degenerative changes of the capillary wall and its epithelial lining, varying in degree from fatty infiltration and hyaline droplet degeneration to complete necrosis, and (3) epithelial proliferation and occasional leukocytic accumulation. The acute alteration of the tubular parenchyma evidenced by fatty infiltration, hyaline degeneration and necrosis was never lacking. In several instances, smaller and larger areas of infarction with anemic necrosis took place. Atrophy of the convoluted tubules varied in intensity corresponding to the degree of stroma proliferation. This was never limited to the surface of the cortex, but involved equally the entire cortical zone.

Routine examination of the other organs showed that the small arteries of the spleen were severely atherosclerotic and narrowed in six cases, those of the pancreas in four cases. With these organs omitted, similar changes were seen but seven times in all the viscera in all the cases. The arterioles of the pancreas were hyalinized and narrowed ten times, once arteriolonecrosis was found. Those of the spleen were

similarly involved only five times. In all the other organs in all the cases, marked arteriosclerosis was found but five times. A cellular intimal thickening similar to that in the kidneys occurred in only four cases. Involvement of the choroid, however, was revealed in every case examined. These choroid changes consisted not only in this cellular intimal proliferation but in severe arteriole hyalinization in every case and actual arteriolar necrosis in one instance.

The tabulation of changes noted by us as existing in the small vessels elsewhere than in the kidneys is in accord with similar observations of other authors in connection with hypertensive states (Fahı,²⁰ Heixheimer,²⁷ Fishberg²⁸). Just as they found that arteriosclerosis affected the vessels of the pancreas and the spleen most frequently after those of the kidneys, so, too, we observed a similar relationship and frequency in these organs with regard to the described changes in the small vessels. It must be emphasized that the involvement of the small and smallest arteries was never general.

Multiple necrosis of the spleen due to degenerative vascular obliteration was first reported by Feitis²⁹ in two cases of chronic interstitial nephritis associated with uremia. Lubarsch³⁰ and Hosoi³¹ published identical observations, in their cases there existed also a vascular renal disease. Similar lesions in the pancreas have been recorded in only a few instances (Roessle,³² Engel³³).

COMMENT

It is evident that our observations conform with those in a group of cases that were first reported by Volhard and Fahı as "Kombinations Form". Within recent years, the term "malignant nephrosclerosis" has been generally accepted in the German literature. In the American literature, Bell and Clawson³⁴ briefly referred to nine cases of the same type, terming them "chronic hypertension with acute uremia,"

27 Heixheimer, G. Zur Frage der Arteriosklerose, *Centralbl f allg Path u path Anat* **33** 111, 1923.

28 Fishberg, A. M. Anatomic Findings in Essential Hypertension, *Arch Int Med* **35** 650, 1925.

29 Feitis, H. Ueber multiple Nekrosen in der Milz, *Beitr z path Anat u allg Path* **68** 297, 1921.

30 Lubarsch, O., in Henke and Lubarsch (footnote 20, 1927, vol 1, p 448).

31 Hosoi, K. Multiple Necrosis of the Spleen, *Arch Path* **6** 26, 1928.

32 Roessle, R. Beitrage zur Kenntnis der gesunden und der kranken Bauchspeicheldruse, *Beitr z path Anat u z allg Path* **69** 163, 1921.

33 Engel, T. Zur Pathologie der Fettgewebs und Pankreasnekrose, *Inaug Diss*, Frankfurt am Main, 1921, cited from Henke and Lubarsch (footnote 20, 1929, vol 5, p 307).

34 Bell, A. T., and Clawson, B. J. Primary (Essential) Hypertension, *Arch Path* **5** 939, 1928.

while Fishberg³⁵ for such cases employs the term "malignant phase of essential hypertension" (see also Sternberg³⁶). The term "malignant hypertension" was used by Keith and Wagner³⁷ to designate a morbid condition characterized by progressive severe hypertension and neuroretinitis. This term may properly be applied to our cases also, particularly in their clinical course before signs of renal insufficiency intervened. However, as renal insufficiency developed in our cases, it is suggestive that they represent the terminal phase of malignant hyper-

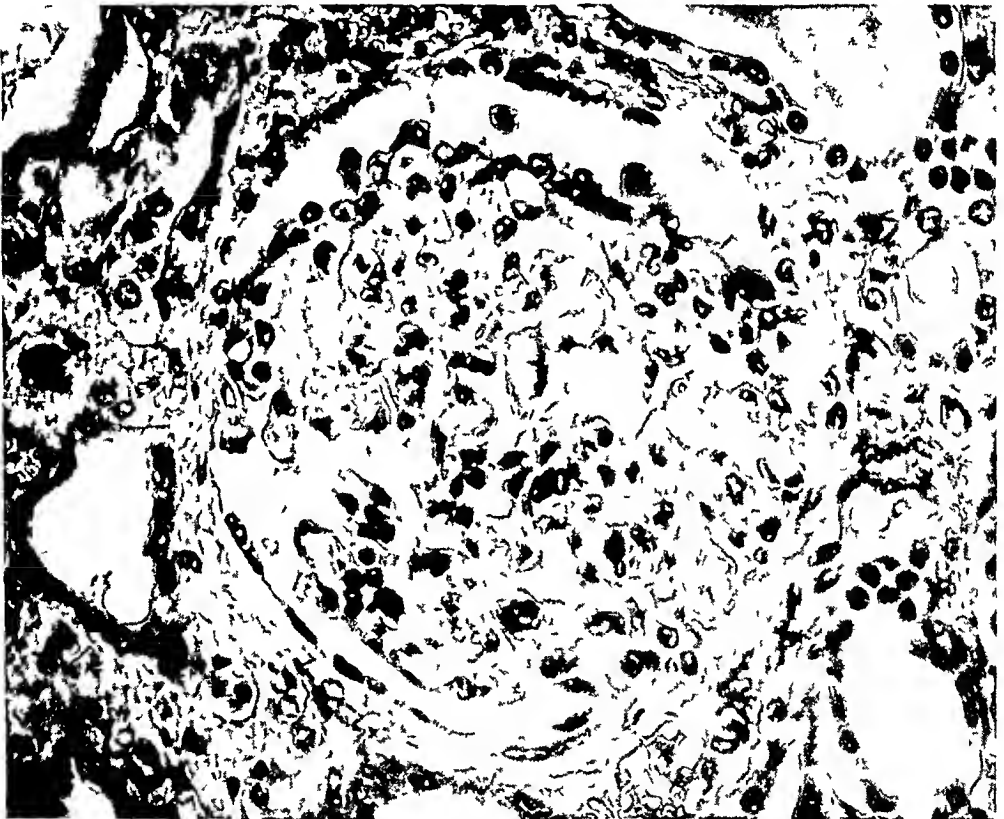


Fig 11 (case 1)—Glomerulus showing fusion of capillary loops, epithelial desquamation, fatty infiltration (foam cells) and thickening of basement membranes

tension. This point of view is supported by the fact that Keith, Wagener and Kernohan,³⁸ too, came on renal insufficiency in a number of their cases.

³⁵ Fishberg, A. M. *Hypertension and Nephritis*, Philadelphia, Lea & Febiger, 1930.

³⁶ Sternberg, B. *Thrombo-Angioneurotic Changes of the Kidneys in Chronic Nephritis*, *Arch. Int. Med.* **44**: 272, 1929.

³⁷ Wagner, M. P., and Keith, N. M. *Cases of Marked Hypertension, Adequate Renal Function and Neuroretinitis*, *Arch. Int. Med.* **34**: 374, 1924.

³⁸ Keith, N. M., Wagner, H. P., and Kernohan, J. W. *The Syndrome of Malignant Hypertension*, *Arch. Int. Med.* **41**: 141, 1928.

The microscopic features that permit a differentiation of these cases from other vascular, or from inflammatory renal, diseases are (1) arteriolonecrosis and extreme cellular intimal thickening of the larger interlobular and so-called arcuate arteries, and (2) degenerative, proliferative and slight exudative focal glomerular lesions. The question arises as to the relative importance of these alterations and their correct pathogenic interpretation.

Focal glomerular alterations characterized by fusion and necrosis of capillary loops, endothelial swelling and epithelial proliferation and

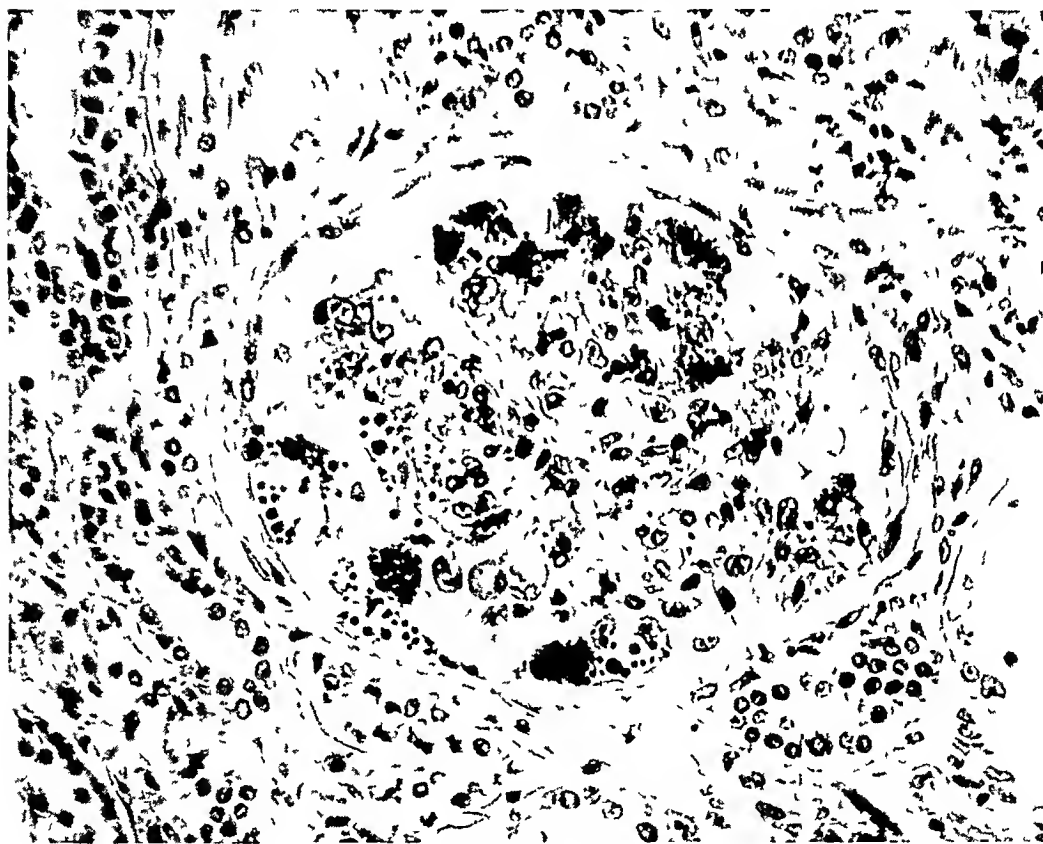


Fig 12 (case 2)—Glomerulus showing epithelial proliferation and severe hyaline droplet degeneration

desquamation, even with occasional crescent formation and slight accumulation of leukocytes within the capillaries, are a constant feature in the microscopic observations (figs 11, 12, 13 and 14). These glomerular lesions exactly correspond with the descriptions and pictures given by Fahr, even in details. For instance, the hyaline droplet formation of the glomerular epithelium stressed by him in his cases of malignant nephrosclerosis was never missed in our cases. Fahr considered all these changes as pathognomonic of nephrosclerosis with renal insufficiency. We, however, found sporadically analogous glomerular changes in cases of vascular renal diseases in which neither the clinical nor the

chemical examination of the blood revealed any evidence of a decreased secretory capacity of the kidneys. Similar observations were reported recently by McGregor³⁹. In these sporadic instances, death was due to cerebral hemorrhage or to cardiac insufficiency or to an intercurrent disease. It is clear that these cases could not have been considered as benign decompensated nephrosclerosis, in which, according to Fahr,²⁰ occasional inflammatory glomerular changes are produced by the irritating action of retained metabolites. Therefore, we believe that the proliferative, degenerative and exudative alterations of the glomeruli are



Fig. 13 (case 2) —Epithelial proliferation and desquamation, hyaline droplet degeneration and accumulation of leukocytes within the loops

not specific for the vascular renal diseases with functional insufficiency. Because occasionally inflammatory glomerular changes were seen in cases without renal insufficiency it seemed important to us to learn how frequently such lesions were present in our cases with renal insufficiency. Differential counts revealed an average of only 10 per cent glomerular involvement. This seems to us proof that the focal glomerulitis cannot play a significant part in the causation of the renal insufficiency.

³⁹ McGregor, L. Histological Changes in the Renal Glomerulus in Essential (Primary) Hypertension, *Am J Path* 6 347, 1930

The next question is whether we should consider these alterations as an evidence of a defensive inflammation in the sense of Aschoff⁴⁰ or as an expression of some other disturbance. The great majority of the malpighian corpuscles showed, according to our description, in every case, a conspicuous anemia of the capillary tufts. It seems logical to ask whether the ischemia, that is, inadequate blood supply, could be the cause not only of the degenerative but also of the proliferative alterations in the glomerular epithelium and of the slight leukocytic reaction as well. With this in mind, we examined many aseptic renal infarcts

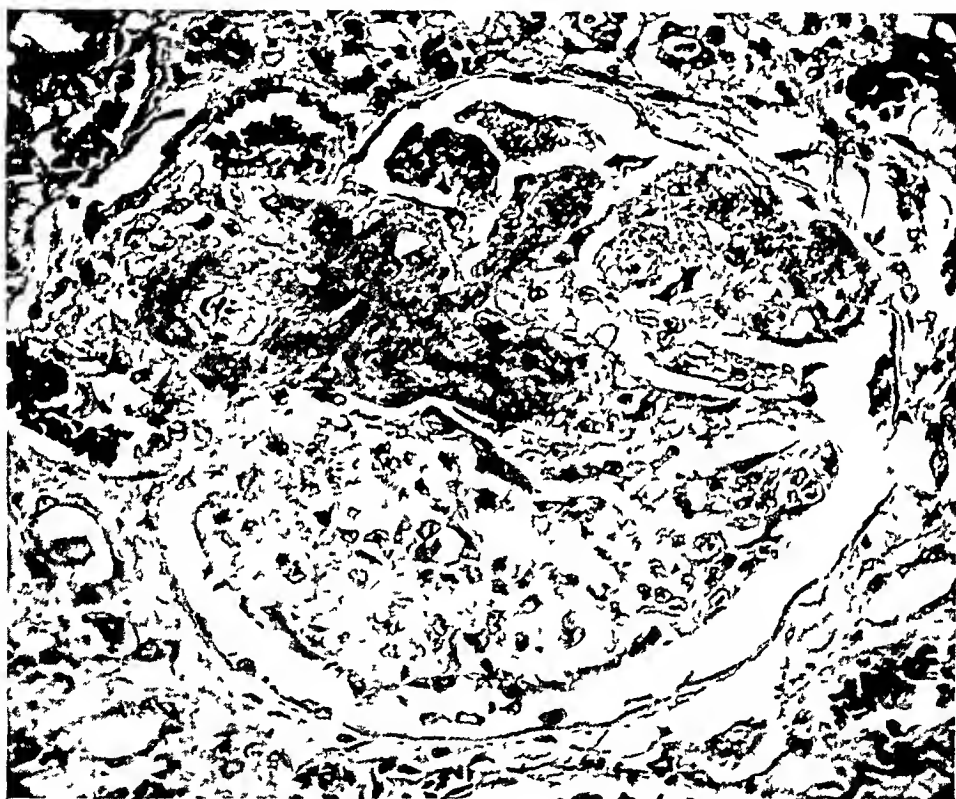


Fig 14 (case 3) —Glomerulus showing the necrosis of loops and afferent artery and fusion of loops

In their periphery, we saw, indeed, occasionally glomeruli that in every respect resembled the inflammatory glomeruli seen in our diseased kidney material. The ischemic origin of the former cannot be denied. These glomeruli also showed fatty and hyaline droplet degeneration in the glomerular epithelium in combination with the cell proliferation and occasional accumulation of leukocytes (figs 15 and 16).

Having demonstrated that ischemia alone can produce these glomerular changes, we strongly suspect that an ischemic mechanism is responsi-

40 Aschoff L. *Vortrage uber Pathologie*, Jena, Gustav Fischer, 1925

ble for the identical glomerular alterations seen in malignant nephrosclerosis. We maintain that the epithelial proliferation is a compensatory reaction to the original epithelial damage brought on by inadequate blood supply and that the accumulation of leukocytes within the loops is due to the chemotaxis of the necrobiotic cells, a process similar to that seen in the vicinity of aseptic infarcts. This explanation on the basis of ischemia has been urged by Jores¹², Lohlein²⁵ and Volhard,¹⁸ but controverted by Fahr²⁰ and von Mueller⁴¹.

Like Fahr and other authors, we found that the vascular lesions were the most conspicuous and characteristic alterations. The necrosis

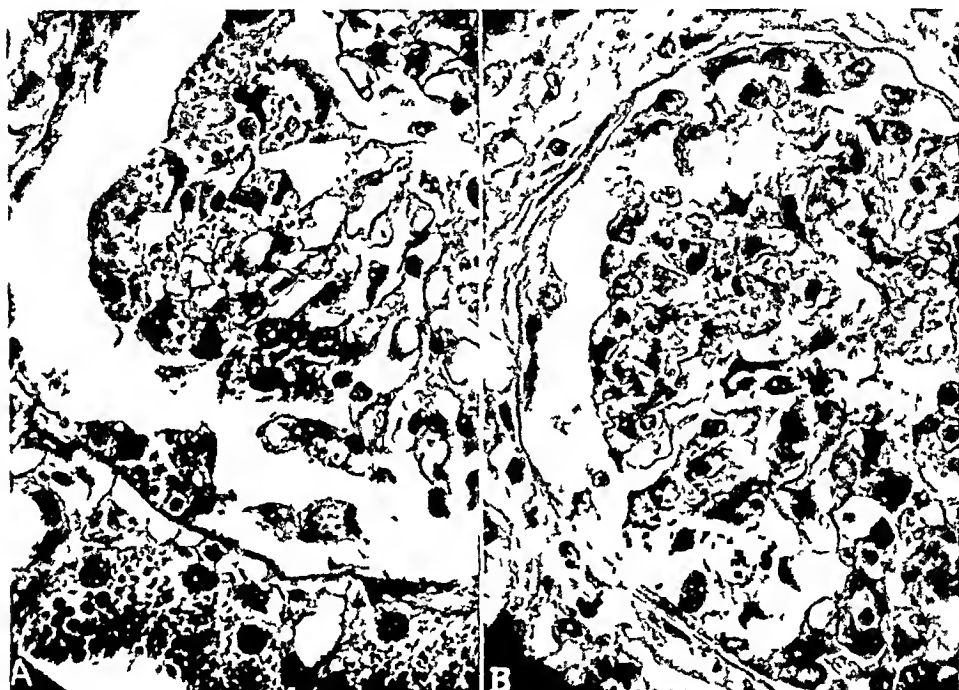


Fig 15—Glomeruli in the vicinity of an anemic infarct (in a case of aneurysm of the left ventricle). *A*, showing hyaline droplet degeneration of the external and internal glomerular epithelium and of convoluted tubules, and *B*, epithelial proliferation and hyaline droplet degeneration.

of the arterioles (vasa afferentia and distal portions of the interlobular arteries) can be sharply distinguished from the simple hyalinization. The indistinct limitation of the vessel wall, the aneurysmal dilatations and the impregnation of the vascular wall by red blood cells and the nuclear disintegration make it easy to distinguish one process from the other (fig 17). Sudan stain, though it obscures the characteristic differential signs, is of great importance because it reveals the extreme

⁴¹ Mueller, F. von. Veröffentlichungen aus dem Gebiete des militäre Sanitätswesens, Berlin, A. Hirschwald, 1917, vol. 65, p. 45.

fatty degeneration of the arteriolar wall. The absence of leukocytic infiltration within and around the blood vessels is the second important feature of the necrotizing vascular lesions. On this point, our observations differ from those described by Fahr²⁰ and Huckel,¹² who emphasized the inflammatory reaction. Therefore we cannot follow Fahr, who believed that the arteriolar necrosis in malignant nephrosclerosis is identical with the necrotizing arteriolitis, as it occurs occasionally in subacute glomerulonephritis. The lesions in the latter disease always show a more or less extensive zone of leukocytic infiltration and fibrin

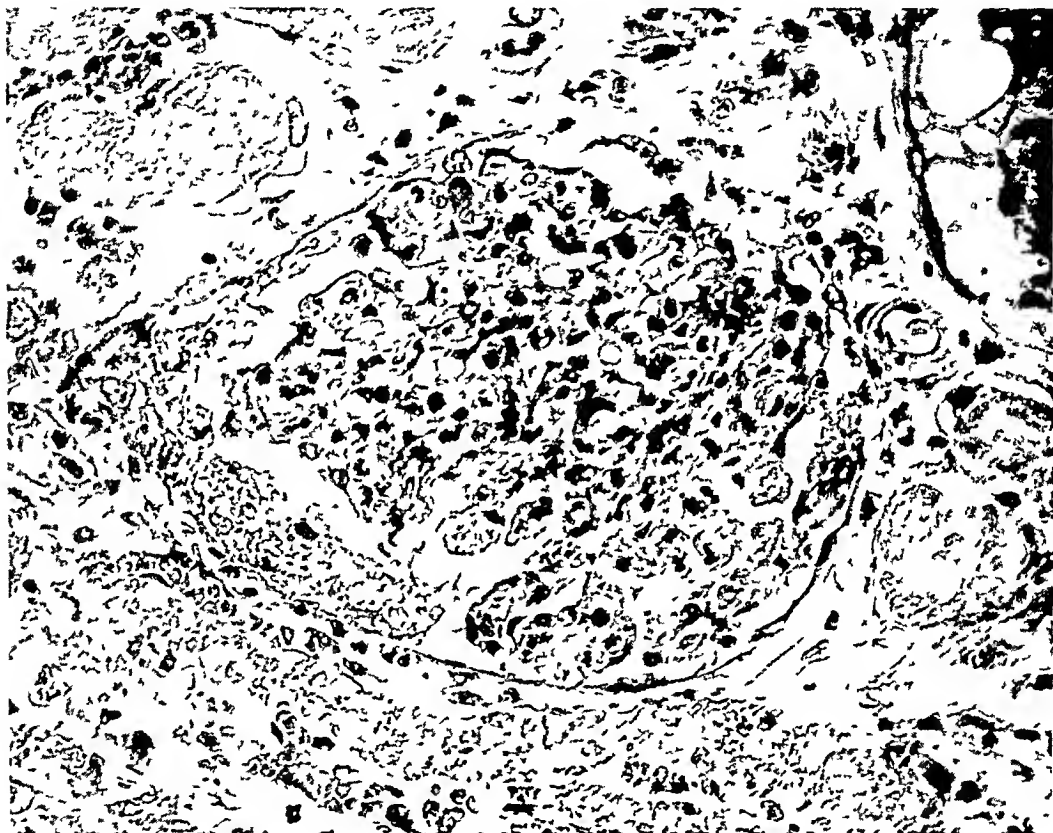


Fig 16—Glomerulus in the vicinity of an anemic infarct (in a case of carcinoma of the cecum) showing epithelial proliferation and desquamation and many leukocytes within the capillaries

within the adventitia, these were never found in our cases. Furthermore, the fatty degeneration here is not as constant as in the necrotized arterioles in our cases. We found fatty degeneration always present and inflammatory changes always absent in the necrotizing arterioles in our cases of malignant nephrosclerosis. We therefore believe that the process is primarily degenerative and is an expression of a severe grade

42 Huckel, R. Beitrage zur malignen Nephrosklerose, Virchows Arch f path Anat 276 447, 1930

of arteriolosclerosis. There is no doubt that the arteriolonecrosis is a constant and conspicuous feature of this group of cases with renal insufficiency, and it therefore serves as a valuable diagnostic criterion in the pathologic picture. For a long time we believed that it existed only in these cases. However, after prolonged investigation, we discovered arteriolonecrosis of the same type in cases of nephrosclerosis with severe arterial hyalinization in which there was not the slightest sign of renal insufficiency (fig 18 *A*). It is true that this arteriolonecrosis is found only in an occasional vessel. Nevertheless, its occurrence under these circumstances proves that vascular necrosis cannot be pathognomonic of nephrosclerosis with renal insufficiency. Of course, the cause of the extreme degenerative vascular disease will

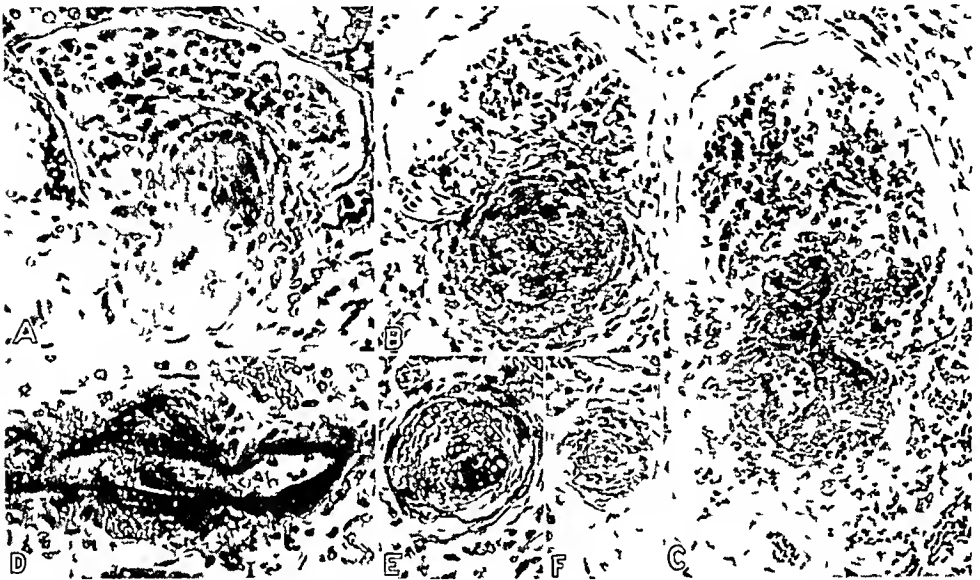


Fig 17—Arteriolar lesions from cases of malignant sclerosis, showing various phases of arteriolonecrosis. The wall is impregnated with red blood cells, which appear black in the reproduction, but there is no other cell infiltration. *A*, hyalinization of afferent vessel with beginning necrosis, evidenced by impregnation of vascular wall by red blood cells, *B*, aneurysmic dilatation and massive impregnation of wall of afferent vessel, *C*, rupture of necrotic afferent vessel, with perivascular hemorrhage, *D*, longitudinal section showing hyalinized vascular wall with necrosis and aneurysmic dilatation, *E* and *F*, cross-sections of intraparenchymal arterioles showing impregnation by red blood cells.

remain obscure as long as the cause of atherosclerosis in general is not known. However, in our opinion, it is likely that ischemia plays an important rôle as a secondary factor. We suggest this conception because we found arteriolonecrosis also in the periphery of aseptic renal infarcts (fig 19).

The extreme narrowing of the entire vascular bed of the renal cortex is of the utmost importance in the pathogenesis of the cases presented

here (fig 20) The frequent occurrence of anemic infarcts and small foci of tubular necrosis is due to focal thrombotic occlusion of severely damaged small blood vessels. The same cause is responsible for the multiple necrosis of the spleen and pancreas in three observations. The general interference with the glomerular circulation is apparent from the conspicuous anemia and collapse of the capillaries which is a significant feature of our observations. The occurrence of congested glomeruli seemingly contradicts this contention. In such instances, however, serial sections disclosed an obliteration of the afferent vessel at some point in its course (fig 7). This is sufficient proof that the tufts could have been filled only by retrograde passage of blood from the venous side.

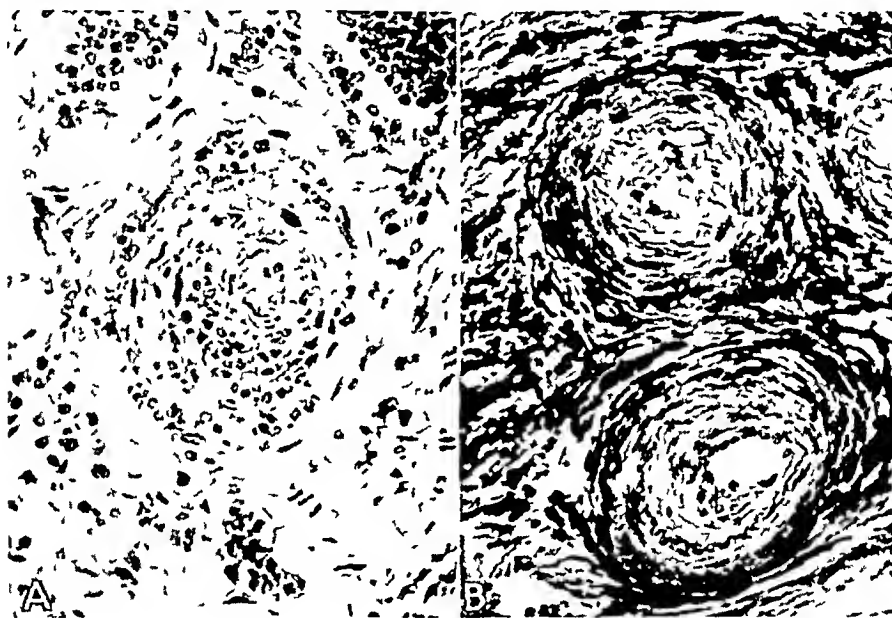


Fig 18—*A*, arteriolonecrosis in the kidney in a case of hypertension with fatal cerebral hemorrhage. *B*, the cellular intimal proliferation in the choroid in the same case.

The engorgement of the intertubular capillaries corroborates this contention. Furthermore, we have shown that the much disputed focal glomerulitis may be considered as a reactive phenomenon caused by ischemia. We believe that the arteriolonecrosis also is partly determined by the insufficient blood supply of the peripheral portions of the vascular tree. That constriction of the vascular bed takes place has been demonstrated by the renal injections of Bachr and Ritter,⁴³ in cases of the type here presented. These authors showed that the lumen of the interlobular arteries was impermeable to a barium-gelatin mixture which could pass the normal ramifications of the cortical vessels up to the

⁴³ Bachr, G. and Ritter, A. S. The Arterial Supply of the Kidney in Nephritis, Arch. Path. 7: 458, 1929.

capillaries. It is not difficult to realize that the insufficient blood supply of the cortex seriously affects renal function. This conception is upheld by the striking fact that the kidneys in our observations showed neither extreme atrophy nor diffuse acute glomerular alteration. In fact, at the first glance, one is surprised to find an apparent incongruity between the severe functional damage and the state of preservation of the renal parenchyma.

The question now arises as to the nature of this vascular lesion. The constriction of the lumen is caused, as we observed in every case, by a cellular proliferation of the intima, the breadth of which exceeds

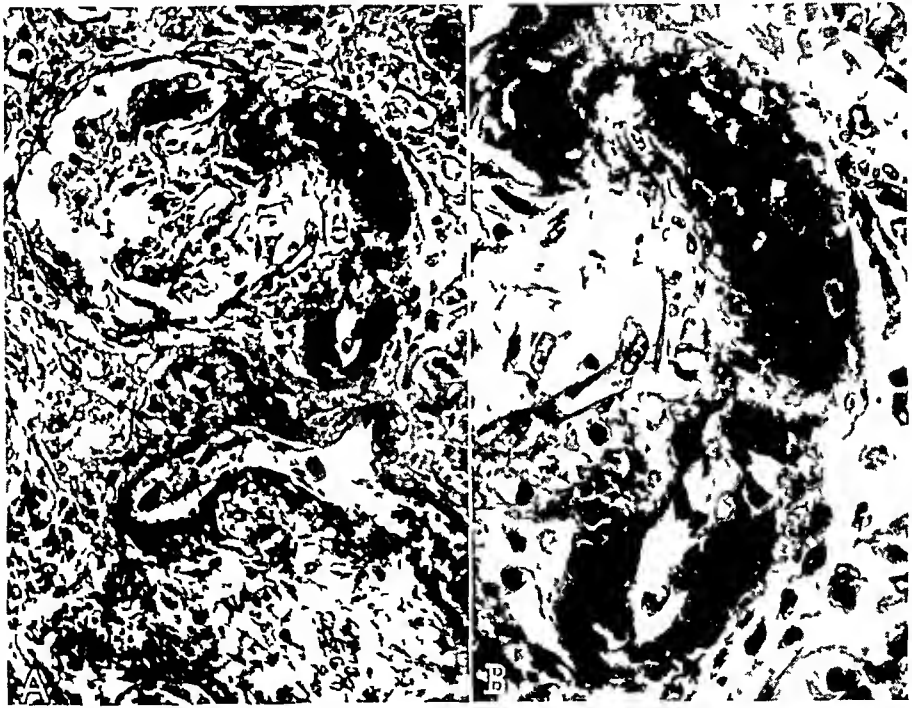


Fig 19—*A*, necrosis of the vas afferens in the vicinity of an anemic infarct (in the same case as the lesions depicted in figure 15) *B*, same under higher magnification. Note the hemorrhagic impregnation of the wall.

by far that of the media. The cells are fibroblasts, which often show a reticulated arrangement, and mononuclear cells with a large amount of fat (foam cells) (fig 21). Between the cells, one encounters fine fibers that stain red with van Gieson's and blue with Mallory's connective tissue stain. Often there is in addition a distinct ground substance which in hematoxylin-eosin preparations takes a bluish color resembling the blue hue of embryonal connective tissue. The internal elastic lamella forms an uninterrupted delicate line separating the thickened intima from the media. This, however, holds only for the smaller branches. The larger vessels often show an outer zone of thickened intima which is denser and contains less cells but more collagen fibers.

In sections showing elastica, this zone presents numerous coarse concentric elastic fibers characteristic of elastica lamellation, whereas the inner zone of the intima shows only occasional fine elastic fibrils. There

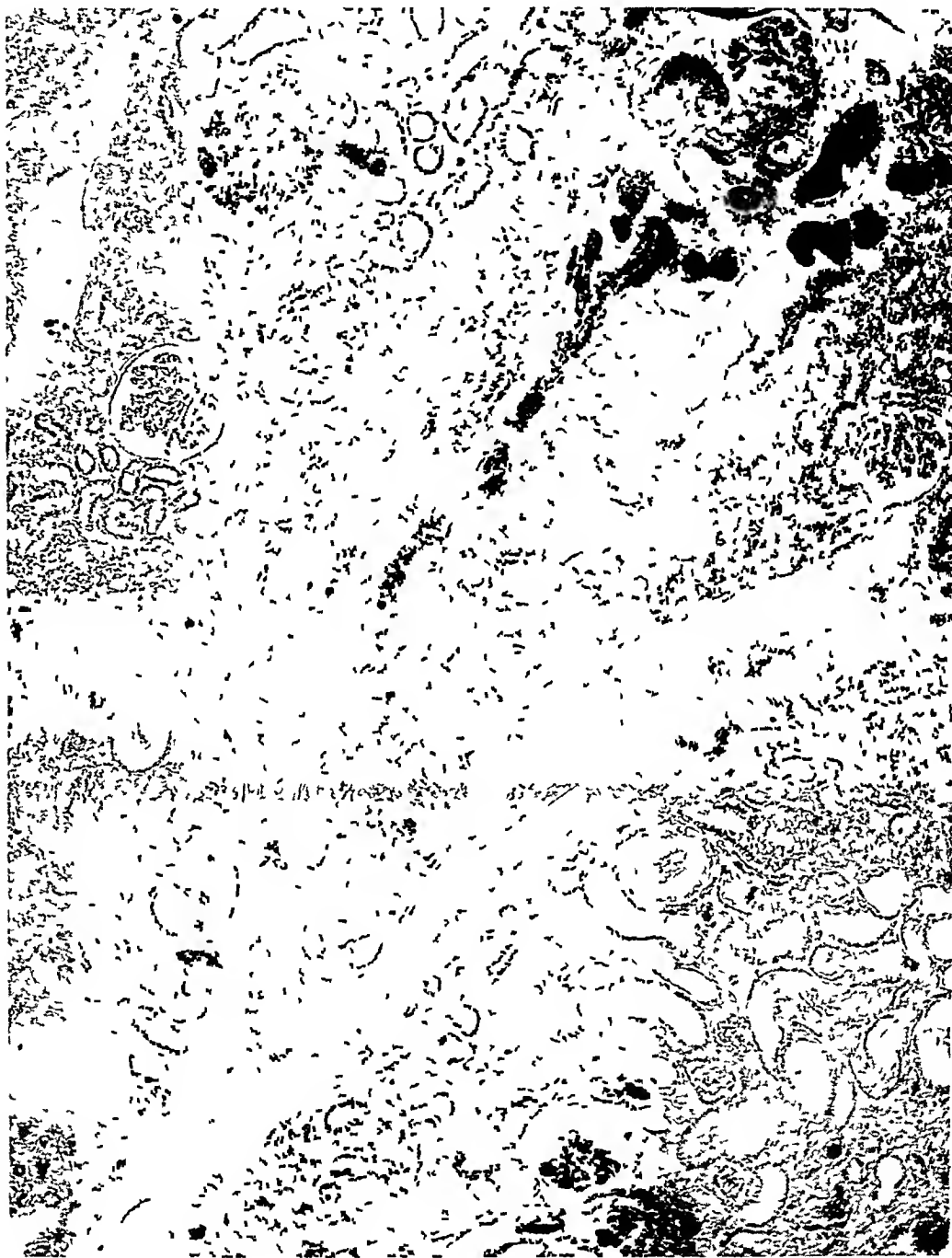


Fig. 20—Ramification of an interlobular artery showing narrowing of the lumen by cellular intimal thickening, fatty infiltration and necrosis of the arteriolar endings and vasa afferentia. The glomerular lesions are anemia and hemorrhagic infarction due to complete closure of the afferent arteriole. Sudan-hematoxylin stain was used.

are always cross-sections and longitudinal sections of vessels that present marked elastica lamellation and connective tissue proliferation with marked narrowing of the lumen, which differ in no way from the familiar picture of simple atherosclerosis. These conspicuous vascular lesions (fig 21) conform fully with the descriptions and figures of Fahl, who attaches great importance to them. These lesions Fahl designated as productive endarteritis, and he held that they are of inflammatory origin. It is our opinion that these vascular changes are not inflammatory, and therefore we must analyze the condition in greater detail.

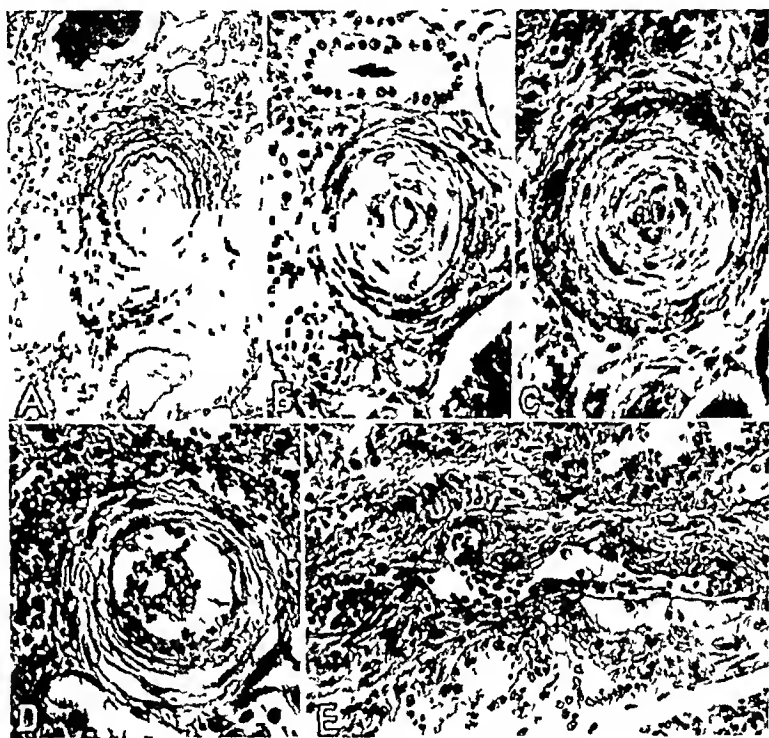


Fig 21—A, B and C, various pictures of the extreme obliteration of the lumen of the interlobular arteries by cellular intimal thickening. Note the xanthophagocytic cells (foam cells) below the endothelium in D and E and the fine newly formed elastic fibers in A.

Connective tissue intimal proliferation differing from atherosclerosis because of the absence of an elastic hyperplastic external zone occurs as is well known, in various pathologic vascular conditions. Friedlander⁴⁴ described alterations of the small vessels in chronically inflammatory territory and termed them endarteritis obliterans. One encounters such pictures daily in chronic peptic ulcers of the stomach, chronic cholecystitis, chronic pulmonary suppuration, etc. Although

⁴⁴ Friedlander C. Ueber Arteritis obliterans, *Centralbl d med Wissensch* 14 65, 1876.

the alteration of the intima is the most conspicuous feature of the process, the other coats of the vessel are also involved. The physiologic obliteration of the lumen of the ductus arteriosus or of ligated vessels is brought about by endothelial and fibroblastic proliferation. Damage to the outer coats of the vascular wall, such as trauma, mesenteritis or periaenteritis, causes a reactive intimal proliferation often even beyond the affected area of the external wall of the vessel. The actual existence of a primary and isolated productive endarteritis is still controversial. It is clear that in our observations none of the mechanisms mentioned applies to the thickening of the intima. The inflammatory reaction of the stroma of the kidney, though generally present in our cases, is so clearly a reaction to the severe degenerative parenchymatous changes produced by the ischemia that it cannot be the cause of the vascular constriction. This is also clear because the vascular lesions are distributed independently of the inflammatory infiltration of the stroma, and because their intensity bears no relation to the severity of the inflammation of the stroma. Inflammatory lesions in the media or in the adventitia of the cortical arteries were always absent, as proved by serial sections, and could not have produced a reactive proliferation of the intima. The intimal thickening of the interlobular arteries in secondary contracted kidneys has been considered by several authors as being the result of the glomerular fibrosis (Fishberg,⁴⁵ and Bach and Ritter⁴³), analogous to the endarterial obliteration proximal to an amputation or a ligation. If this were true, vascular lesions should be found in every case of chronic glomerular nephritis and also in amyloid contracted kidneys, this is not the fact. However apart from this argument, because glomerular fibrosis was rare in every case, for our cases this origin of the intimal proliferation cannot be considered at all. For the aforesaid reasons we believe that the term productive endarteritis should not be applied to the intimal proliferation seen in our cases because it implies the assumption of a pathogenesis that does not hold true for these vascular alterations

The absence of a lamellated internal elastic layer in the smaller vessels is apparently the only feature that differentiates the lesion in question from atherosclerosis. Sudan stain reveals mostly fatty degeneration of the newly formed layer of cellular connective tissue which appears sometimes as a concentric ring between media and intima. We have mentioned that in some instances and particularly in those in which more advanced glomerular fibrosis occurred, we encountered newly formed elastic fibers in the outer zone of the thickened intima. Fahn²⁰ described similar observations and referred to them as a com-

⁴⁵ Fishberg, A. M. The Arteriolar Lesions of Glomerulonephritis, Arch Int Med **40** 80, 1927

bination of elastic hyperplastic thickening of the intima and endarteritis (his cases 51, 52, 54 and 55) It seems to us that these pictures allow different interpretations, if the deductions of Hueck⁴⁶ regarding the morphologic development of atherosclerosis are followed His ideas center around the conception that the intima retains throughout life the embryonal mesenchymal character of a reticulated cytoplasmic syncytium Under normal conditions, the meshes of the reticulum are collapsed The first phase of atherosclerosis consists in an opening up of the reticulum whereby nuclei float from the "accessoria" (media and adventitia) into the cytoplasmic syncytium This leads then to a thickening of the intima, which appears in cross-sections and longitudinal sections as a richly nucleated cytoplasmic network The cytoplasm around the nuclei is condensed and becomes differentiated into nuclear cytoplasmic territories and cytoplasmic ground substance (endoplasma and ectoplasma of Hansen⁴⁷) Immediately a fibrillar differentiation begins within the ground substance, leading to the formation of an argyrophil fiber, the silver or mesenchymal fiber of Ranke⁴⁸ Connective tissue and elastic fibers are formed by impregnation of the fibrillar differentiation products by collagen or elastin This takes place only gradually In contradistinction to Jores,⁴⁹ Hueck maintained that the elastic lamellation does not occur by splitting up of the internal elastic lamella, but by actual new formation of elastic fibers from the cytoplasmic ground substance In its first stage, the atherosclerotic intima would appear, therefore, as a mere cellular layer with beginning fibril formation between the mutually connected cells This statement is not unsupported, in fact, Jores himself, in his classic monograph⁴⁹ in 1903, seventeen years before Hueck, stated that in the early phases of atherosclerosis he occasionally came on a pure cellular intimal thickening above an area of fatty degeneration at the border-line between media and intima Our observations seems to coincide fully with the conceptions of Hueck as outlined here We have emphasized the cellular constitution of the intimal proliferation (fig 21 B and C) and have mentioned the delicacy of the collagen fibers, also the embryonal appear-

46 Hueck, W Anatomisches zur Frage nach Wesen und Ursache der Arteriosklerose, Munchen med Wchnschr **67** 535, 1920, Ueber das Mesenchym, Beitr z path Anat u z allg Path **66** 330 1920

47 Hansen, F C C Ueber die Genese einiger Bindegewebssubstanzen, Anat Anz **16** 417, 1899

48 Ranke, O Neue Kenntnisse und Anschauungen von dem mesenchymalen Syncytium und seinen Differenzierungsprodukten unter normalen und pathologischen Bedingungen, Sitzungsbd Heidelberg Akad d Wissenschaft, math-naturwissensch Kl, sec B, 1913, Abhandl 3, Zur Theorie mesenchymaler Differenzierungs- und Impregnations Vorgange, *ibid*, 1914, Abhandl 2

49 Jores, L Wesen und Entwicklung der Arteriosklerose auf Grund anatomischer und experimenteller Untersuchungen, Wiesbaden, J F Bergmann, 1903

ance of this connective tissue. With Bielschowsky's stain, the differentiation of the fibrils is more pronounced than with Mallory's or van Gieson's stain. This means that the impregnation by collagen is as yet not very advanced. We have, however, noted that often the connective tissue formation has progressed further and that the intimal proliferation in some instances seems to be much denser, containing far more collagen fibers. The appearance of elastica lamellation in the outer zone of this intimal layer (fig 21 A) indicates the further development of the process, that is to say, a later phase of the atherosclerosis initiated by a purely cellular (better, cytoplasmic) intimal proliferation. The elastica differentiation represents a later phase of this process, we found it

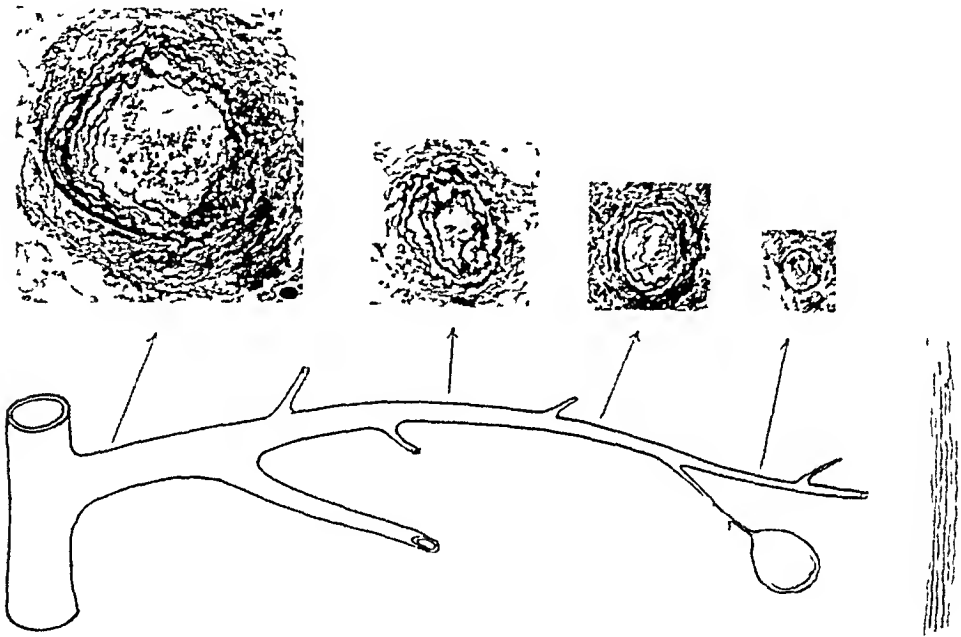


Fig 22—The entire course of an interlobular artery, showing the various phases in the development of atherosclerosis in one and the same vessel

especially in cases of more advanced glomerular fibrosis, namely, those instances that indicate a longer duration of the pathologic vascular processes. Atherosclerosis is generally of slow development, and one is accustomed to seeing only the end-stages with the fully developed elastic hyperplastic connective tissue intimal thickening. The fact that we are able to demonstrate all the phases of the process often in a single specimen (fig 22) indicates that the process develops rapidly. We believe that we are warranted in asserting that the vascular alterations in malignant nephrosclerosis formerly and usually designated as endarteritis are in reality an accelerated form of atherosclerosis, in other words an acute variation of the usually slow atherosclerosis of the small arteries

Although the etiology of this accelerated form is no clearer than that of atherosclerosis in general, there is a special interest in speculating on the etiologic relationship in this type between our strictly morphologic observations and the conceptions put forth by Volhard. He believed that the alteration of the interlobular arteries in similar cases is dependent on a permanent vascular constriction which leads to an ex vacuo proliferation of the endothelium distally to the constriction. This proliferation acts to adjust the vascular lumen to the diminished volume of the circulating blood. Our studies show that an initial cellular phase is transformed by the gradual development of collagen and elastic fibers into atherosclerosis. On the other hand, we sometimes encountered in hypertension a simple atherosclerosis which disclosed a few small vessels presenting pictures of cellular intimal thickening resembling that described extensively in foregoing paragraphs (fig 18 B). If vascular spasms are actually responsible for the initiation of the intimal thickening which, according to our opinion, is the first phase of atherosclerosis, it is conceivable that the etiologic difference between the two forms of the atherosclerotic processes lies in the severity and especially in the permanence of the vascular constriction (Volhard⁵⁰). It is conceivable that a constitutional or acquired angiospastic factor could be the reason for the severity and specially for the acceleration of the vascular process which is the outstanding characteristic for the differentiation between vascular diseases of the kidney with and without functional insufficiency. We believe that the acceleration of the atherosclerotic process in the small cortical arteries of the kidneys is the essential pathogenic principle in our cases and leads subsequently to ischemic damage of the arterioles and glomeruli. Our observations are in accord with Lohlein's idea that the tempo of the atherosclerotic process distinguishes both forms of vascular nephrosclerosis. We also hold with Jores that the vascular alterations in these cases with renal insufficiency are far more extensive than in simple nephrosclerosis without functional damage. We, however, believe that the intensity of the lesion in the interlobular arteries is of primary importance, and not that in the vasa afferentia.

However, it would be a mistake to disregard the observations of Fahr and Huckel of definite inflammatory vascular changes in cases of identical clinical course and identical gross anatomic appearance. We have two cases to illustrate this point.

CASE 17—*History*—A. C., a white man, aged 42, married, a salesman, was admitted to the hospital on Aug 10, 1927. The family history was irrelevant. The childhood history was unimportant. Three years before, the patient felt fatigued. Albumin was found in the urine. The patient was told to cut down his

⁵⁰ Volhard, F. Der arterielle Hochdruck, Verhandl. d. deutsch. Gesellschaft f. inn. Med. **35** 134, 1923.

protein diet, which he did not do. He had occasional occipital headaches. Three weeks before, he noticed a bad taste in his mouth and had paroxysmal pains in the left lumbar region. His vision became blurred. He vomited twice in the two weeks previous to admission.

Examination—On admission, he appeared to be chronically ill, was subicteric and showed puffiness of the eyelids. The breath was urinous. The heart was enlarged. The fundi showed neuroretinitis. The blood pressure was 200 systolic and 114 diastolic.

The urine was decreased in amount and contained albumin (++), the sediment contained granular casts, white blood cells and red blood cells. The con-

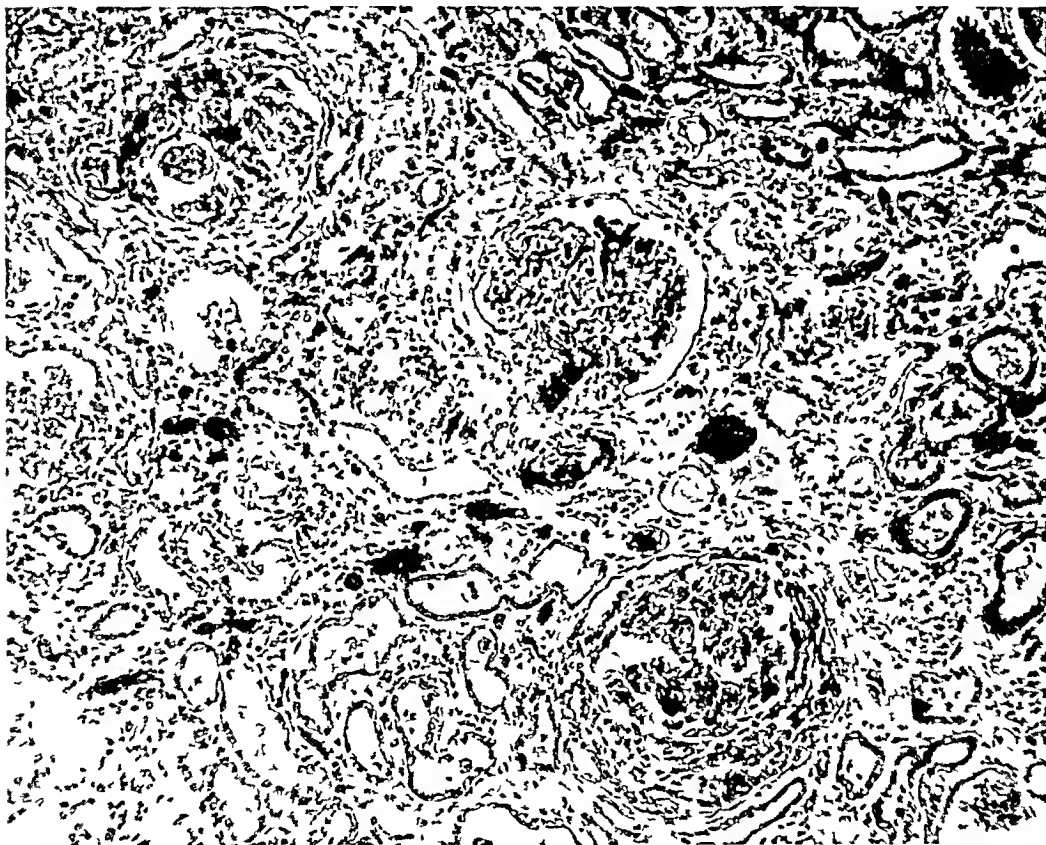


Fig. 23 (case 17)—Three glomeruli with inflammatory changes in one field and arteriolonecrosis

centration was from 1006 to 1011. The phenolsulphonphthalein excretion was 10 per cent in four hours. The urea nitrogen of the blood was 91 mg, and the uric acid, 84 mg per hundred cubic centimeters. The Wassermann reaction was negative. The blood count showed hemoglobin, 44 per cent, red blood cells, 2,570,000, white blood cells, 8,900, polymorphonuclear leukocytes, 83 per cent, lymphocytes, 15 per cent, monocytes, 1 per cent, and eosinophils, 1 per cent.

Course—The patient received a transfusion. Afterward he began to vomit uncontrollably. He died suddenly on August 16, after a paroxysm of coughing.

Necropsy—Eight hours after death, necropsy was performed by Dr Klemperer. Permission to open the head was not obtained. The right kidney weighed 220 Gm, the left, 200 Gm. The capsule stripped easily revealing numerous fine

yellowish granules and red pinpoint-sized hemorrhages. On section, the cortex appeared narrowed and the markings indistinct with a mottling of yellow and gray spots. The renal artery did not show changes.

Microscopically, nearly all of the glomeruli showed changes characteristic of an intracapillary subacute glomerulonephritis as nuclear increase, many polymorphonuclear leukocytes, fusion of loops with each other, as well as with Bowman's capsule, and proliferation and desquamation of glomerular epithelium with occasional crescent formation (fig 23).

The stroma was diffusely increased and infiltrated with lymphocytes, polymorphonuclear leukocytes and occasional plasma cells. The tubules contained desquamated epithelial cells, leukocytes and granular casts. The epithelial cells often

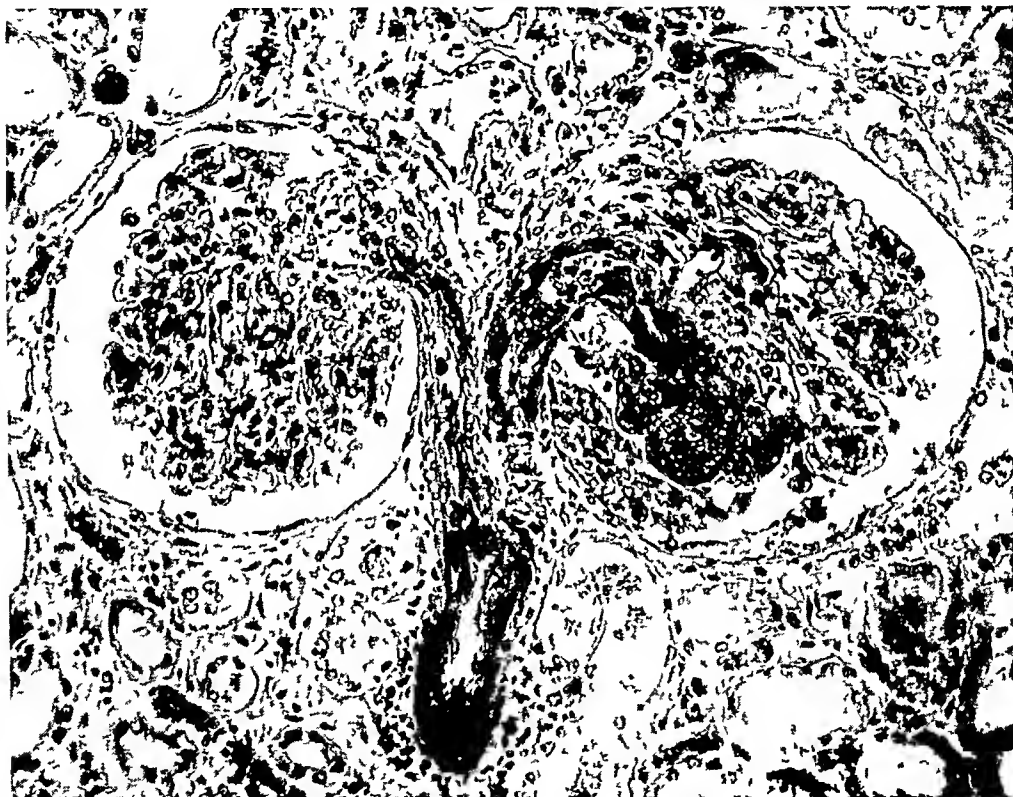


Fig 24 (case 17) —Necrosis of an afferent vessel, with perivascular leukocytic infiltration

showed hyaline droplets and fat. They were frequently flattened and had lost their characteristics. The most conspicuous change was necrosis of the capillary loops, arterioles and small branches of the interlobular arteries. The necrotic vessels were surrounded by an infiltration of polymorphonuclear leukocytes, polyblasts and lymphocytes (fig 24). The perivascular infiltration and necrosis were occasionally so marked that the picture simulated that found in larger vessels in periarteritis nodosa. The interlobular arteries often showed thickening of the intima, which was infiltrated by polymorphonuclear leukocytes, lymphocytes and polyblasts (fig 25). The larger vessels showed atherosclerosis. Sudan stain revealed only moderate fatty degeneration of the arteriolar wall. Bacterial stains were negative.

Diagnosis—The diagnosis was subacute glomerulonephritis with arteriolonecrosis, hypertrophy of the left ventricle, edema of the lung, and ascites

CASE 18—History—E J, a colored woman, aged 40, married, a housewife, was admitted to the hospital on April 2, 1927. The family history was irrelevant. The patient had always been well, but two years before admission, she was told that she had high blood pressure. She was advised to keep to a diet, which was, however, not strictly adhered to. For some time she had had dyspnea on moderate exertion. For three months she had had frequent headaches. She became pregnant and vomited frequently within the first months. Two weeks before admission, she went to bed because of an aggravation of her symptoms,

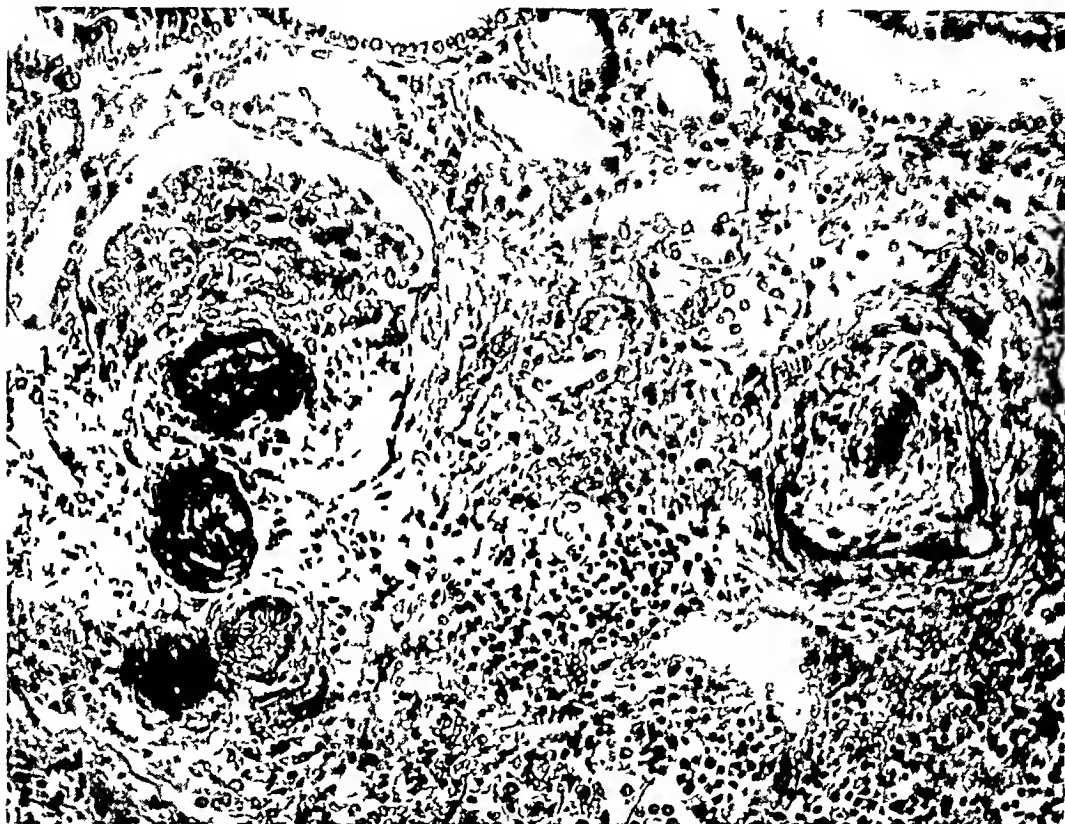


Fig 25 (case 17)—Arteriolonecrosis and arteritis of an interlobular artery. Note the inflammatory cells within the proliferated intima.

and a few days later she aborted. Then she became drowsy, fell into stupor and was admitted to the hospital in coma.

Examination—She had no fever. She had Cheyne-Stokes' respiration and a urinous breath. Her blood pressure was only 124 systolic and 70 diastolic, but she was already in extremis. Her urine contained albumin (+), the sediment, clumped blood cells and granular casts.

The urea nitrogen of the blood was 169 mg per hundred cubic centimeters. The white blood cells numbered 15,400, the polymorphonuclear leukocytes, 86 per cent, and the lymphocytes, 12 per cent. The Wassermann reaction was negative.

Course—The patient died on April 3.

Necropsy—A few hours later necropsy was performed by Dr Klemperer. The right kidney weighed 175 Gm, the left, 160 Gm. The capsule stripped with fair ease, revealing a finely granular surface, studded with an enormous number of irregular hemorrhages varying in size from that of a pinpoint to that of a pinhead and larger and numerous yellow pits. On section, the cortical markings were obscured by numerous small infarcts and hemorrhagic flecks. The small arteries were prominent.

Microscopically, the cortex was studded with numerous areas of necrosis which left little unaffected renal parenchyma. In such areas, however, some glomeruli were large, with delicate engorged capillary loops, other glomeruli, however, showed a few necrotic loops, nuclear increase and epithelial proliferation. Here

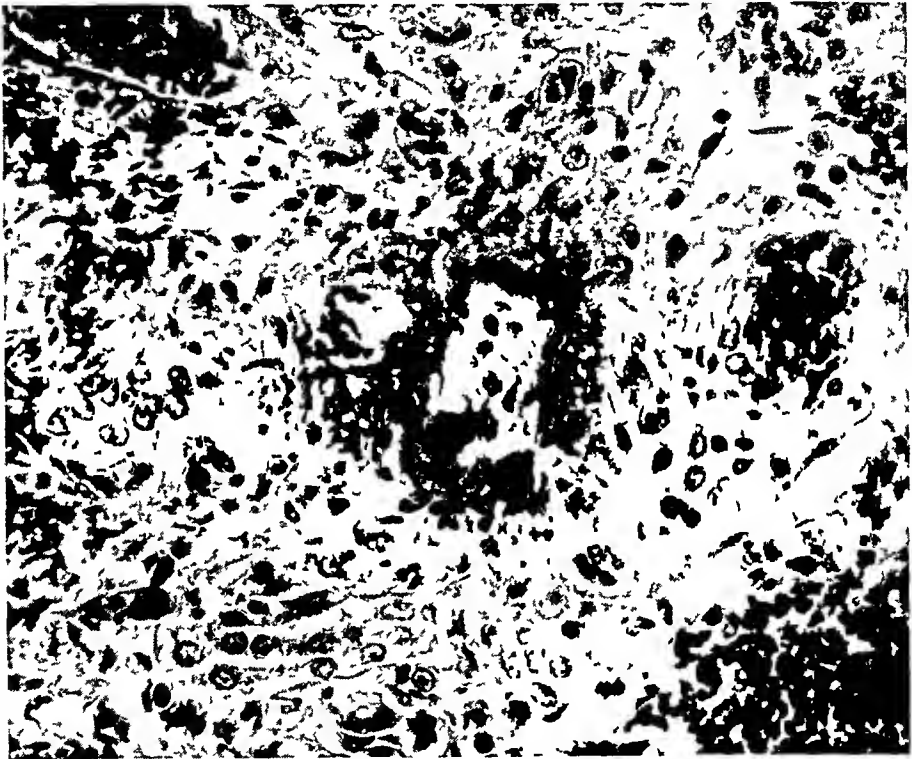


Fig 26 (case 18)—Arteriolonecrosis with perivascular cellular infiltration and fibrin infiltrating the wall extending into the adventitia

the arterioles showed marked hyalinization and necrosis. The blood vessels supplying the areas of necrosis showed necrosis and severe perivascular infiltration with polymorphonuclear leukocytes and lymphocytes (fig 26). They were often thrombosed. Bacterial stains were negative.

The spleen and the liver showed marked hyalinization of the arterioles. The pancreas and the suprarenal glands showed an extreme degree of arteriosclerosis. Within the pancreas, several larger arteries showed necrosis with infiltration of the vascular wall and the adventitia by polymorphonuclear leukocytes and thrombosis (fig 27). The pancreatic tissue around the vessel was necrotic. Within the suprarenal gland, one artery showed an identical picture.

Diagnosis—The diagnosis was arteriosclerosis and arteriolonecrosis of the kidneys with multiple infarctions, circumscribed necrosis of the pancreas, hypertrophy of the heart, especially of the left ventricle and status after abortion.

The clinical course in these cases resembled that in our other cases. After an antecedent stage of hypertension of several years' duration, the middle-aged patients suddenly developed symptoms of renal insufficiency and died in uremia. The gross morphology of uncontracted kidneys with conspicuous hemorrhages was also in agreement with the observations in our other cases.

The arterial lesions were also the outstanding features of the microscopic picture. These differed, however, from those previously described in the character of the necrosis, for we found severe inflam-

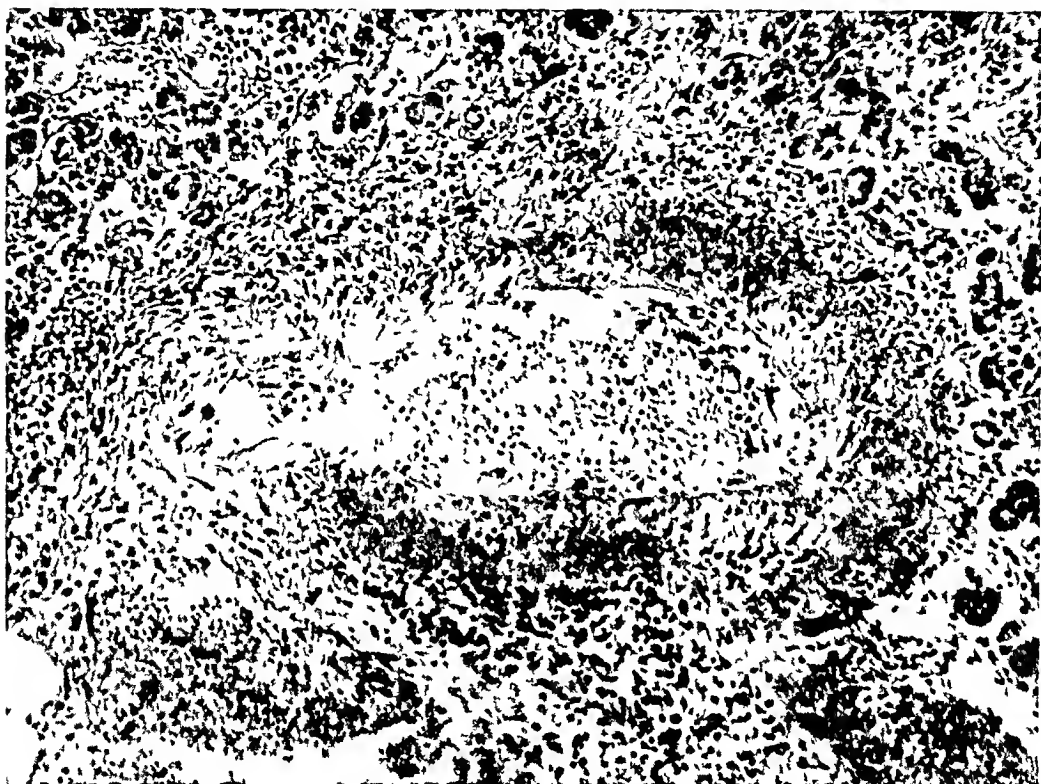


Fig. 27 (case 18) —Pancreatic artery showing necrosis of media and inflammation as in periarteritis nodosa

matory reaction within and around the vessels. These alterations could truly be designated as necrotizing arteriolitis, endarteritis and periarteritis. The further difference consisted in a diffuse glomerulitis in the first case and the presence of a necrotizing arteritis in the pancreas and suprarenals in the second case. It seems significant that we encountered the necrotizing arteritis only in these two cases in which there was also present a morbid process recognized generally as toxic in origin. We refer to the subacute glomerulonephritis in case 17 and to the hyperemesis gravidarum in case 18. In both cases there were shown severe hyalinization of the arterioles and advanced atherosclerosis of the small arteries, widely distributed in case 18. It is possible that this antecedent

vascular damage made the arterioles and arteries more vulnerable to the influence of toxin and in this way acted as another determining factor for the vascular necrosis (Heixheimer²¹) Of course, we appreciate that necrotizing arteriolitis is not so rarely found in subacute glomerulonephritis However, we have encountered it only in cases of so-called "stormy course" of Lohlein⁵¹ with the characteristic histologic picture of extracapillary glomerulonephritis The fact that the glomerulitis in case 17 was mainly intracapillary, therefore of the milder type, supports the implication that the antecedent vascular damage is an important factor

A comparison of our observations and the reports in the literature showed clearly that cases of identical clinical course present a definite difference in the type of the essential vascular alteration A careful analysis disclosed the degenerative nature of the arteriolonecrosis and of the so-called endarteritis of the small cortical arteries in the overwhelming majority of our observations On the other hand, one cannot doubt the inflammatory nature of the periarteritis and endarteritis of the interlobular arteries and the necrotizing arteriolitis of the vasa afferentia in the cases reported by Fahr and Huckel and in one of our own cases This clearly indicates that the anatomic picture of the kidneys in the malignant phase of hypertension must be divided accordingly into an accelerated atherosclerotic and an arteritic form

ETIOLOGY

Fahr postulated a toxic etiology for his cases and considered, mainly, syphilis, lead and rheumatic polyarthritis as the causative agents Huckel's cases were also syphilitic In one of our cases of the arteritic form there was evidence of a toxic factor, though not of the same nature as Fahr contended, which superimposed on previously damaged vessels might have been responsible for the severe vascular lesion In the other cases, however, only one of the patients had a positive Wassermann reaction and he had no syphilitic organic lesion, another patient had previously had lead poisoning None of the patients had a history of either polyarthritis or an acute or a chronic valvular disease suggestive of rheumatism This conspicuous difference in the etiology of our series is a further foundation for our view in distinguishing two forms of malignant nephrosclerosis Some of our patients had suffered from occasional headaches a long time before the onset of their severe symptoms Of course, we cannot maintain that these were an evidence of an angiospastic migraine We would therefore like to recommend that similar cases should be investigated as cautiously and carefully as pos-

⁵¹ Lohlein, M Ueber die entzündlichen Veränderungen der Glomeruli der menschlichen Nieren, Arbeiten a d path Institut zu Leipzig, 1908

sible for antecedent angiospastic symptoms. We offer the suggestion that such a constitutional or acquired factor may be responsible for the accelerated atherosclerotic type of malignant nephrosclerosis.

DIFFERENTIAL DIAGNOSIS

It is evident that in the differential diagnosis we have to consider only cases with hypertension and uremia without edema. In essential hypertension of longer duration, almost invariably arteriosclerosis of the vasa afferentia is present, combined with atherosclerosis of the arcuate and interlobular arteries. This vascular alteration produces atrophy of the parenchyma which may reach such an extent as to cause excretory insufficiency. Such instances have been designated by Fahr as benign decompensated nephrosclerosis. The decompensation may be absolute, owing to parenchymal destruction so extensive that the remaining renal rest is unable to take care of the waste products, or it may be relative, owing to the simultaneous cardiac insufficiency. In such instances, the renal destruction is not advanced enough to cause functional insufficiency as long as an increased cardiac action compensates by increasing the velocity of the perfusion fluid. In both events, however, the decrease in the size of the kidneys and the more or less advanced glomerular fibrosis is sufficient evidence of the prolonged vascular alterations which had gradually caused the atrophy. In contradistinction to this picture, the kidneys in the malignant phase of hypertension are generally not shrunken. They show, however, in addition to a diffuse irregular flat granulation, characteristic ecchymoses, as gross evidence of the hemorrhage due to the severe vascular lesions.

The glomerular fibrosis is never marked. The extreme diffuse alteration of the small cortical vessels, as described, together with the secondary ischemic phenomena of arteriolonecrosis and focal glomerulitis are the features that histologically distinguish the accelerated atherosclerotic form from the simple, gradually developing renal atherosclerosis and arteriosclerosis with renal insufficiency. It is clear that the arteritic form of the malignant phase of hypertension cannot be confused with simple atherosclerosis.

Chronic glomerulonephritis with atrophy, the secondary contracted kidney, offers in the majority of cases no differential diagnostic difficulties. The development of conspicuous vascular changes, however, may cause, in some instances, grave doubts as to the proper interpretation. This holds true especially for cases in which the glomeruli do not show diffuse involvement, but in which the alterations of the arcuate and interlobular arteries are striking. The vascular lesions in chronic glomerulonephritis are commonly divided into true atherosclerosis and endarteritis. It has been generally accepted within the last years that

the explanation of the development of atherosclerosis in chronic glomerulonephritis lies in the permanent increase in the blood pressure. The so-called endarteritic process, however, has been explained as the result of the chronic inflammation or of the destruction of parenchyma. Volhard assigns to this process the pathogenesis mentioned heretofore, namely, a permanent vascular spasm. It seems to us just as impossible to differentiate these vascular lesions in secondary contracted kidneys from those found in the malignant renal phase of hypertension, as it is impossible to distinguish between the atherosclerosis in chronic glomerulonephritis and that in essential simple hypertension. Since we believe that the so-called endarteritis in the former condition is only an accelerated form of atherosclerosis, we are of the opinion that its occurrence in chronic glomerulonephritis indicates only a more rapid tempo in the development of the atherosclerosis, but not a different pathogenesis. This conception is supported by the fact that degenerative arteriolonecrosis is also encountered occasionally. The histologic differentiation of such cases of chronic glomerulonephritis complicated by acute atherosclerosis of the interlobular arteries is sometimes exceedingly difficult. One can depend on the extent of the inflammatory glomerular involvement, which exceeds in these instances that encountered in the malignant renal phase of hypertension. Nevertheless, the interpretation may sometimes be subjective. It is imperative to examine many sections from various regions of the kidneys before reaching a diagnosis. Fortunately such cases are not too frequent. Among thirty-seven cases of chronic glomerulonephritis and malignant nephrosclerosis, we found only two that were doubtful pathologically.

CLASSIFICATION OF VASCULAR RENAL DISEASE IN HYPERTENSION

The extent and the intensity of the renal vascular alteration are responsible for two forms of hypertensive disease, one with and one without renal insufficiency. Accordingly, we may classify the concomitant renal process in three groups.

- 1 The slow progressive atherosclerosis of the vascular tree, primarily without contraction (*atherosclerosis renum initialis lenta*), secondarily with subsequent gradual atrophy of the renal parenchyma (*nephrocirrhosis atherosclerotica lenta*, with three subgroups according to the degree of contraction—*incipiens*, *progressa* or *gravis*).

- 2 The rapidly progressing diffuse atherosclerosis (*nephrocirrhosis atherosclerotica accelerata*, with only the first two subgroups according to the degree of contraction).

- 3 The inflammatory diffuse vascular lesion superimposed on an antecedent atherosclerosis (*nephrocirrhosis atherosclerotica et arteritica* with the same subgroups as in 2).

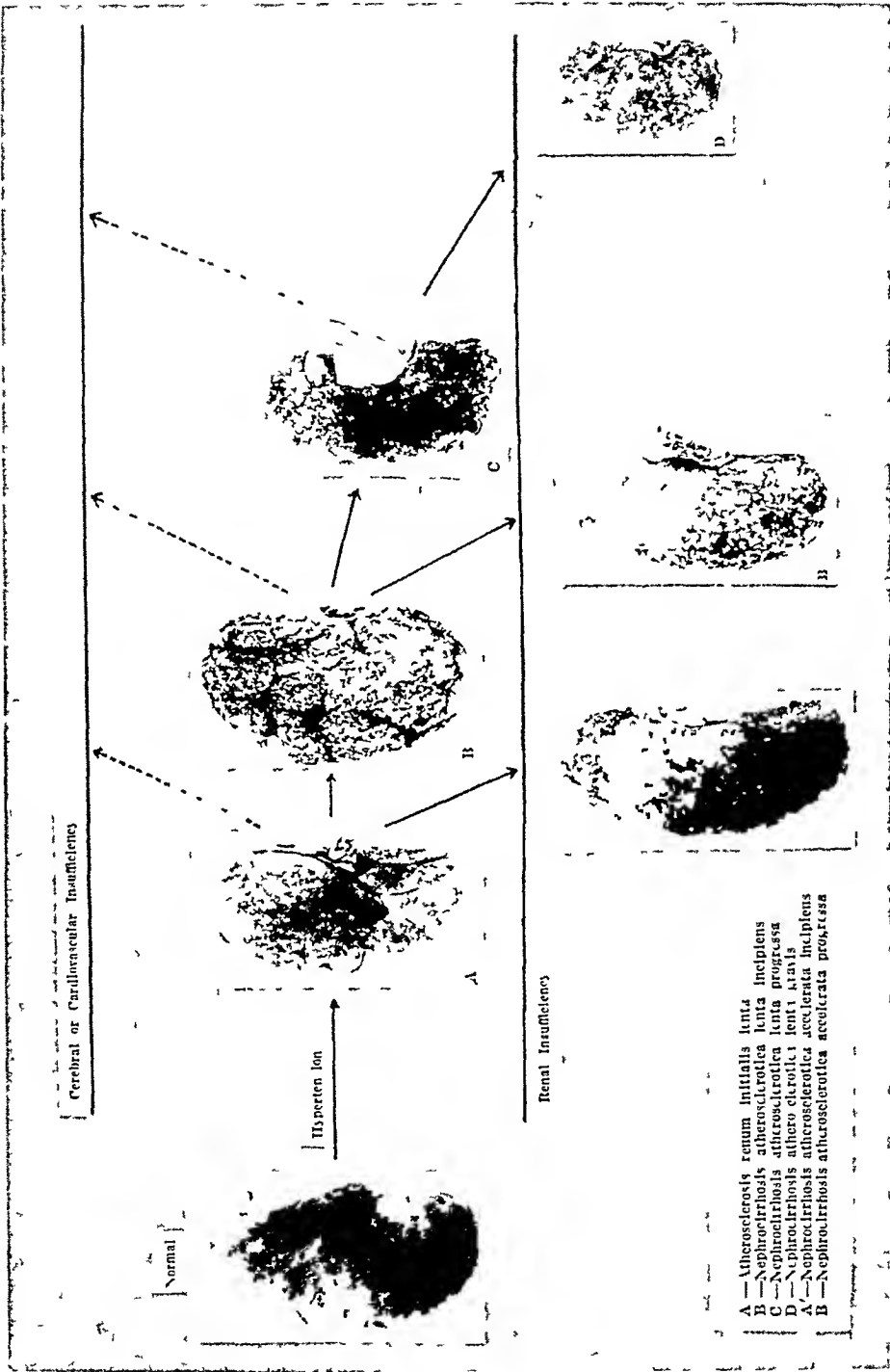


Fig 28—Schema of renal lesions in hypertension illustrated by actual cases The arteritic form was not tabulated because there are no macroscopic features distinguishing it from the accelerated atherosclerotic group

A differentiation of arteriolosclerosis and arteriosclerosis has been omitted because both processes have an identical pathogenesis and are too frequently combined to be separated by terminology (fig 28)

The schema here set forth indicates that the atherosclerotic process may become accelerated at any phase of group 1, causing renal insufficiency. It is, however, conceivable that this change in the tempo may occasionally not be so rapid and that such instances may form an intermediate group between groups 1 and 2. This assumption is suggested by cases 11, 12, 15 and 16, with more advanced atrophy than was found in our other observations but with less contraction than in the advanced forms of the lenta group.

SUMMARY

Essential hypertension with renal insufficiency is associated either with (1) the slowly progressing type of atherosclerosis manifesting a gradual constriction of the vascular bed and subsequent pronounced destruction of the functioning parenchyma, or (2) with a more rapidly developing vascular change in which severe renal atrophy is absent.

The latter form, the malignant renal phase of hypertension, must be divided on a pathologic basis with regard to the nature of the vascular lesions into (1) an accelerated atherosclerotic and (2) an arteritic form.

The rapidly developing obliteration of the vascular bed is responsible for the sudden onset of fatal renal insufficiency.

The etiology of the vascular condition is unknown. It is conceivable and in accord with Volhard's conception that a constitutional or acquired angiospastic factor plays a determining rôle in producing the accelerated atherosclerotic form. The arteritic form is most probably due to the effect of various toxins on vessels that have already suffered a simple degenerative atherosclerosis.

GANGLIONEUROMA OF RETROPERITONEAL ORIGIN

REPORT OF A CASE, WITH BIBLIOGRAPHIC REFERENCES
TO NINETY-THREE SIMILAR TUMORS^{*}

JOSEPH McFARLAND, M D

PHILADELPHIA

H D a white girl, aged 12, was observed to have a gradually enlarging abdomen. When asked about it, she complained of no pain or other disturbance, nor could she in any way account for it. As the enlargement continued, the protuberant abdomen attracted attention more and more, and she was in due course of time charged with being pregnant. Her parents then took her to a physician, who made a careful physical examination that resulted in the discovery of an abdominal tumor not connected with the uterus, which was normal and infantile. As the tumor had apparently grown as rapidly as the fetus for which it was mistaken would have done, malignancy was feared and operation recommended.

This was performed in September, 1915, fifteen years ago, in a hospital in Trenton, N J, by Dr Edward Skillern Hawke, who found and removed a large nodular retroperitoneal mass that weighed about 4½ pounds (2 Kg) and was thought to be a sarcoma.

The tumor, or parts of it, were sent to the laboratory of the State Hospital, where sections were prepared by Miss Mae I Lovett. At that time the pathologist, Dr Frederick Hammond, was in Europe, and had arranged to have slides of tumor tissues sent to me for identification.

I at once recognized the peculiar structure of the tumor and identified it as a "ganglionic neuroma." Miss Lovett, finding that I was interested in the case, sent me additional sections from different parts of the tumor. I thus came into possession of nine mounted slides, two stained with hematoxylin and eosin, two with thionine, one with Mallory's aniline blue, one with Mallory's phosphotungstic acid hematoxylin, one with van Gieson's stain and one by Pal's method.

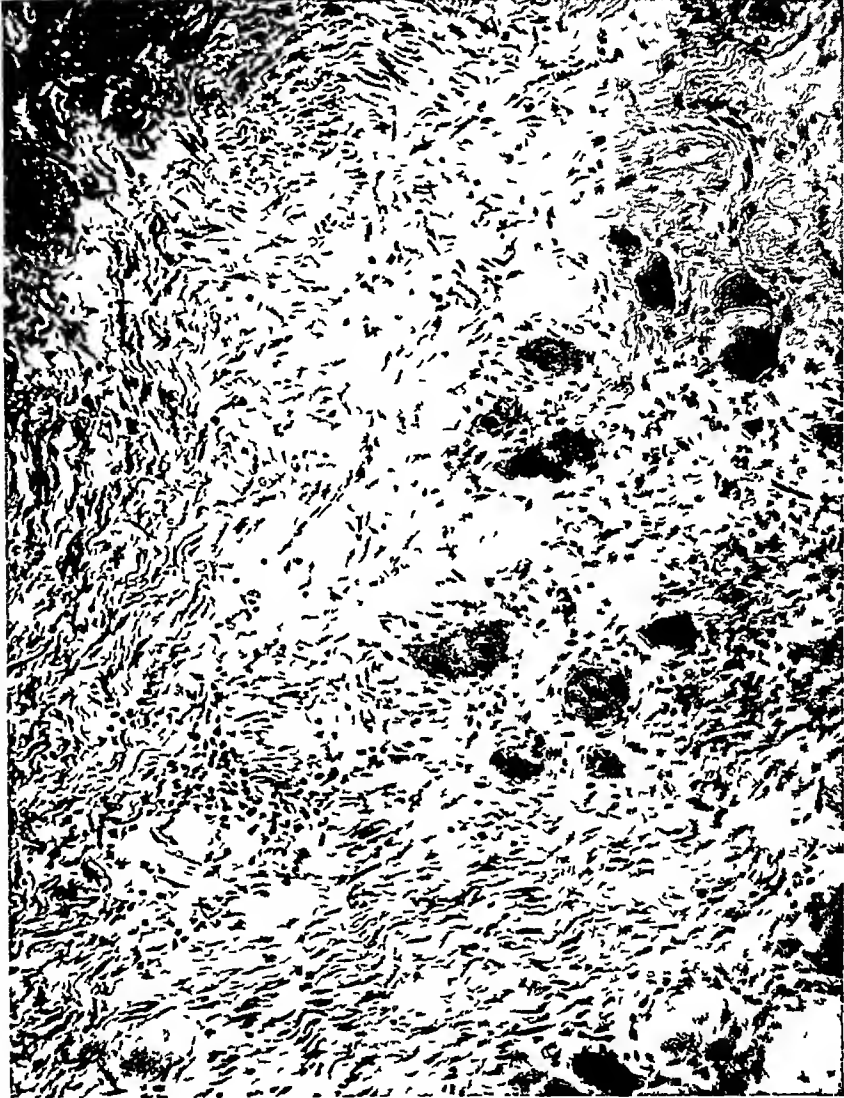
Dr Hammond returned from abroad ill, he soon became incapacitated and gave up his work, so that he was unable to act on my suggestion that he publish the case. A year or two later I wrote to Dr Hawke suggesting that he publish the case, but received no answer. A request for some of the tissue, in order that more sections might be made, resulted in the discovery that the tumor had been thrown away. A later request for the loan of the paraffin blocks was answered by a letter saying that a new technician had taken Miss Lovett's place, and that the change had resulted in a good deal of material having been rejected as no longer useful, probably these blocks had been thrown away, as they could not be found.

From time to time correspondence with Dr Hawke was renewed, with the object of having the tumor recorded, but he never replied, probably because, as was learned from other sources, the subject was very distasteful to him, the patient having died on the third day after the operation.

^{*} Submitted for publication, June 30, 1930.

So the matter dragged along until Dr Hawke died

The surgeon having passed away, the pathologist being permanently incapacitated and entirely uninterested, the technician having resigned and the material having been thrown away, there is no longer any one but myself sufficiently interested in the case or acquainted with it to place it on record



Portion of the tumor showing a bundle of fibers in the lower part, another on the left, and a group of ganglion cells, some of which are in fair condition, while others are in a state of advanced degeneration such as is characteristic of the lesion. The wavy character of the bundles of fibers, together with their reaction to the specific stains, shows them to be a highly specialized type of tissue probably descended from the neuroglia. Although the fibers rarely contain axis cylinders, there is no doubt of their neurogenic origin.

Since 1915 there have been about twenty-eight publications dealing with the ganglioneuromas and reporting new cases, so that the tumor

is much better known than when the case under consideration came under observation. In nearly every one of the contributions there is a complete description of the histologic appearances, sometimes brief, but too often tediously long. It therefore seems unnecessary to burden the literature with another description of the tumor, the photomicrograph that accompanies this report being sufficient guarantee of the correctness of the identification. But those especially interested in ganglioneuromas may be glad to be furnished with a bibliography of the subject, and to that end one is appended. Two works may prove of special value: that of H. R. Wahl, in the *Journal of Medical Research* (30: 205, 1914) in which he deals with all varieties of nerve cell tumors, systematically arranging them, commenting on their relationships and including a lengthy bibliography, and that of J. S. Dunn in the *Journal of Pathology and Bacteriology* (19: 456, 1915), in which much the same ground is covered.

In looking over the more recent contributions, I discovered that the authors just referred to had missed some cases found by later students and that some of the references had been incorrectly given. A complete review of the literature was therefore made. Unfortunately, a few of the references were to papers that proved to be inaccessible, so that although the following list is undoubtedly an improvement on previously published lists, it cannot be said to be perfect.

REPORTED CASES OF GANGLIONEUROMA

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(c) GANGLIONEUROMAS OF RETROPERITONEAL ORIGIN

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- Soyka Ueber den Bau und die Stellung der multiplen Neurome, Prag Vrtljschr 1877, vols 133-135 (Same case as given under Retroperitoneal Ganglioneuromas)
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7 GANGLIONEUROMAS IN LOWER ANIMALS

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Laboratory Methods and Technical Notes

A METHOD FOR STAINING LECITHINS IN SECTIONS *

C M RAMIREZ CORREA, HAVANA, CUBA

The following technic for staining lecithins in sections is useful

Frozen sections are placed in acetone, at room temperature, for from one to twenty-four hours. The sections are washed, and are then placed in sudan-acetone, for a few minutes. Then differentiation, washing, mounting, etc., are done. The nuclei stain as in ordinary sudan sections, the acetone soluble lipids are not stained, and the lecithins stain pale red or orange.

* Submitted for publication, Aug 11, 1930

* From the Sanatorio "La Purisima Concepcion"

Notes and News

Cancer Survey of the United States—According to *Science*, the U S Public Health Service will be able to begin at once its cancer survey, which is to include (1) an investigation of the researches being carried on with respect to control of cancer in various institutions in the United States and abroad, (2) an investigation of existing methods of treatment of cancer with a view to determining and encouraging the use of the best methods of treatment to the exclusion of those that are worthless or fraudulent, (3) the ascertaining of the best methods of increasing the number of physicians skilled in the diagnosis and treatment of cancer, (4) the ascertaining of the best means of educating the public with respect to the signs and symptoms of cancer in early stages in order to prevent neglect and delay in treatment, (5) the ascertaining of the extent to which provision now exists for furnishing optimum treatment for cancer in all sufferers, together with an estimate of what would be needed to make this adequate, and the cost thereof, (6) the collection of any other pertinent data to enable Congress to act advisedly in this matter

Window Method of Studying Living Tissue—The method consists in the introduction of a transparent double wall or window into a small hole in the ear of a rabbit. One side of the window is celluloid or glass and the other mica, living tissue invades the chamber in a transparent layer which can be studied microscopically in vitro under various conditions. The Rockefeller Foundation has granted \$15,000 a year for five years for the perfection and extension of the method

University News, Appointments, Promotions, Resignations, etc—Carl O Gunther, bacteriologist, one of Koch's assistants, and well known to early American students of bacteriology, has died at the age of 75

E D Peasley, formerly of the department of pathology and bacteriology in the University of Iowa, is now pathologist to the Truesdale Hospital, Fall River, Mass

In the school of medicine of the University of Kansas, S D Katz has been appointed instructor and T J Sims, Jr, and O S Randall assistants in pathology. T J Sims, Jr also serves as resident pathologist in the Bell Memorial Hospital

Theodore S Kimball has been appointed assistant pathologist and John L Jackson resident pathologist in the Los Angeles County General Hospital

H P Smith, associate professor of pathology in the University of Rochester, N Y, has been appointed professor of pathology in the University of Iowa

W C Merkle, associate in pathology in the University of Maryland, has been placed in charge of the laboratories of the Union Memorial Hospital in Baltimore

M C Porterfield has been appointed instructor in pathology in the University of Maryland

In the University of California, J F Rinehart has been promoted to assistant professor of pathology and Hermann Becks has been appointed assistant professor in charge of dental pathology

In the University of Nebraska at Omaha, Victor Norall has been appointed resident pathologist in the university hospital, J T Myers, associate professor of bacteriology, has been advanced to professor of bacteriology and public health

Stokes' Tablet—A memorial tablet in honor of William Royal Stokes has been erected in the municipal building in Baltimore by his fellow employes in the health department. The tablet bears the relief portrait of Dr Stokes and this inscription: "To the memory of an able physician and bacteriologist. A lover of art, music and poetry, who died a martyr to the cause of science, contracting psittacosis (parrot fever) in line of duty"

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

NOTE ON THE EFFECT OF REPEATED INTRAVASCULAR INJECTIONS OF HEPARIN
W H HOWELL and C H McDONALD, Bull Johns Hopkins Hosp **46** 365, 1930

The results indicate that a daily injection of a relatively large dose of purified heparin for six consecutive days does not cause any change in the corpuscles of the blood, nor any significant change in the clotting time. There was certainly no indication of a shortening of this time, but rather a slight tendency toward a lengthening. The excess of heparin injected into the blood was removed, at least in part, through the kidneys.

THYROID HEART, A TRANSITORY CONDITION. HENRY M THOMAS, JR, Bull Johns Hopkins Hosp **47** 1, 1930

Two similar cases of exophthalmic goiter with severe myocardial insufficiency are reported. In one case, the patient died after operation on the thyroid gland, while in the other the patient achieved complete clinical recovery. This second case, then representing an extreme form of myocardial insufficiency in thyroid heart disease with auricular fibrillation of more than a year's duration, which went on to subsequent complete recovery, demonstrates clearly that even the most severe intoxication from hyperthyroidism need not produce permanent damage of cardiac function. In the first case, as in most others reported in the literature, although death resulted from heart failure, there was no evidence, pathologically, of significant myocardial damage. These cases, coupled with many others from this clinic, as well as from other clinics, place the burden of proof on those who claim that permanent myocardial damage results from hyperthyroidism.

AUTHOR'S SUMMARY

PHYSIOLOGIC AND CHEMICAL STUDIES FOLLOWING SUCCESSFUL TOTAL GASTRECTOMY FOR CARCINOMA. WALTMAN WALTERS, J A M A **95** 102, 1930

In the case presented here, total gastrectomy was performed successfully for an extensive scirrhous carcinoma of the linitis plastica type. Studies made of the chemical changes in the blood, and of the cell count over a period of four months, do not reveal any appreciable change in the number of erythrocytes, in the hemoglobin content, in the carbon dioxide combining power or in the concentration of blood chlorides or urea. Evidence of a definite alkaline tide has not been found. This observation is of interest, since it has been recognized that, with the secretion of gastric juice in a normal person, the urine tends to become more alkaline. The data so far, in this case, appear to indicate that the lack of a stomach and of its acid-secreting glands has a definite effect on the morning alkaline tide.

AUTHOR'S SUMMARY

VITAL STAINING WITH INDIA INK AND BRILLIANT VITAL RED. J VICTOR, J R VAN BUREN and H P SMITH, J Exper Med **51** 531, 1930

When brilliant vital red is injected into the blood stream of dogs much of it is slowly taken up into numerous phagocytes scattered throughout the tissues ("reticulo-endothelial system" of Aschoff). The rate at which the dye leaves the

blood stream is determined in large part by the action of these phagocytic cells, but the excretion of dye into the bile is also in part responsible for the loss of dye from the plasma. The injection of a small amount of india ink into the blood stream results in lowering the rate at which the dye disappears from circulation. The fact that much of the carbon of the ink is promptly taken up by the phagocytes would lead one to suspect that they were saturated with foreign materials, or "blocked" against the entrance of dye, but it is shown that the ink causes a remarkable inhibition of the excretion of dye into the bile, and this alone seems to account for the longer retention of dye in the blood stream. There is no evidence that any of the retention is due to defective activity on the part of the phagocytes. Thus, prolonged retention of foreign materials in the blood stream cannot be cited to prove "blockade of the reticulo-endothelial system" unless one can rule out such peculiar reactions on the part of excretory organs. It is felt that the literature of "blockade" should be studied with such sources of error in mind.

AUTHORS' SUMMARY

THE EXPERIMENTAL TRANSMISSION OF LEUKEMIA IN MICE MAURICE N
RICHTER and E C MACDOWELL, J Exper Med 51 659, 1930

Lymphatic leukemia has occurred with great frequency in a particular strain of mice which have been inbred by brother-sister matings since 1921. In addition to typical cases of leukemia are others which, because of the absence of leukemic changes in the blood, correspond to "pseudoleukemia" and others which, by the presence of unusually great enlargement of certain lymph node groups, resemble the "leukosarcomatoses" as observed in man. Examinations of the blood of leukemic mice have shown that leukemic blood pictures are not necessarily early in their appearance, nor are they constant. The blood picture may not, therefore, be used as a criterion for the separation of the two diseases (leukemia and pseudoleukemia) but merely indicates different phases of the same condition. Likewise, cases with lesions intermediate between the local growths of "leukosarcomatosis" and the more general lymphatic enlargements of leukemia suggest that these conditions differ only in the distribution of lesions but not in their nature. Lymphatic leukemia occurring spontaneously in this strain may be transmitted to other mice of the same strain, and carried, apparently, for an unlimited number of transfers in animals at an earlier age than that at which leukemia occurs spontaneously. The lesions produced by inoculation correspond to those of spontaneous cases, in that they consist of growths of abnormal lymphoid cells which infiltrate tissues and organs and often appear in the circulating blood. Only minor differences have occurred, some of which are characteristic of certain experimental lines. After repeated transfers, the disease tends to run a more acute course. Among the cases in which transmissions occurred are some without leukemic changes in the blood and many with local growths at the site of inoculation or in certain node groups. The differences in the blood pictures and distribution of lesions (which latter may be influenced to some extent by the method of inoculation) correspond to similar differences which are sometimes observed in the spontaneous cases.

AUTHORS' SUMMARY

THE GRADIENT OF VASCULAR PERMEABILITY PEYTON ROUS, H P GILDING
and FREDERICK SMITH, J Exper Med 51 807, 1930

The permeability of the capillaries in the skeletal muscles of mammals increases progressively along their course and is greatest where they pass into the least venules. The gradient of permeability is too largely independent of functional states to give grounds for the view that it is determined by inherent local differences. Through the gradient opportunity is equalized along the capillary. In the liver lobule this object is accomplished by an artifice of arrangement whereby the blood flow past the cells is increased with their distance from the source of

supply In the urinary bladder the interlacing of capillaries, their progressive widening and a consequent gradual slowing of the blood flow act to achieve the same end Here a gradient of permeability has not been demonstrable Where cells of different sorts are served by a slender capillary, their differing requirements may render unnecessary any provision to equalize their opportunities, but where shortcomings in local maintenance will reduce the efficiency of an entire fabric, as the muscle fiber, and where cells of like character live competitively along the same channel, as in the liver, some arrangement must exist to ensure an even distribution of the services rendered by the blood In situations of the kind last mentioned the immediate environment of the individual cell, the "milieu interne" of Bernard, is not only kept as constant as possible but it must be the same, by and large, for all of the cells The task of serving voluntary muscle is not strictly limited to the capillaries The intrafascicular arterioles and venules act so effectively to sustain the tissue about them that where they run no capillaries are supplied

AUTHORS' SUMMARY

TOTAL WATER AND CHLORIDE CONTENT OF DEHYDRATED RATS T G H
DRAKE, C F MCKHAN and J L GAMBLE, J Exper Med **51** 867, 1930

The circumstances present in upper intestinal obstruction which may be expected to reduce the water content of the body are fasting with water deprivation and a continued loss of secretions into the stomach According to the data obtained from experiments with rats, loss of body water during the first third of the survival period following pyloric obstruction is more than half accounted for by fasting with water deprivation This body water is accompanied by a parallel loss of solids and may be regarded as a waste product of the consumption of body fat, glycogen and protoplasm Its loss does not disturb the percentage of water content of the body tissues The water lost into the stomach is responsible for an actual excess of water reduction over consumption of solids Except in the case of the skin and blood, this excess loss of water is extremely small and produces a reduction of the percentage of water content of tissues which is so slight as to permit the surmise that the water loss here derives entirely from the interstitial fluid of the tissues and that no dehydration of tissue cells occurs The data are, however, not directly informative on this point The total loss of body water during twelve hours following pyloric obstruction was found to be 12.6 per cent of the water content of a control animal More than one fourth (28.3 per cent) of the total body content of chloride ion was found to be lost and was entirely accounted for by the amount of chloride found in the gastric contents Nearly half of the chloride loss occurs from the skin Data are presented which demonstrate that lower intestinal obstruction causes slight, if any, depletion of the water content of the body

AUTHORS' SUMMARY

TOOTH GROWTH IN EXPERIMENTAL SCURVY GILBERT DALLDORF and CELIA
ZALL, J Exper Med **52** 57, 1930

The incisor teeth of guinea-pigs have a constant rate of growth in health Deprivation of vitamin C causes the teeth to cease growing Readministration of the vitamin restores the growth Administration of small amounts of anti-scorbutic substance results in rates of growth roughly proportional to dosage Under standard experimental conditions used in the testing of foodstuffs for anti-scorbutic value, the rate of tooth growth would appear to be a precise indication of the degree of scurvy, being more delicate than the Sherman score, and more constant, as well as more simple, than the Hoyer method Stress in terms of usage appears to exaggerate the scorbutic lesions in the teeth

AUTHORS' SUMMARY

Pathologic Anatomy

THE BLOOD CYTOLOGY OF THE RABBIT LOUISE PEARCE and ALBERT E. CASEY,
J. Exper. Med. **52** 23 and 39, 1930

Observations are reported on the consecutive weekly erythrocyte counts and the hemoglobin contents of the peripheral blood in five groups of normal rabbits, comprising forty-five animals, during a period of twenty months from October, 1927, to July, 1929. The duration of individual group examinations varied from eight to thirty-five weeks. The results are analyzed on the basis of the weekly mean values of each group. On the whole, the erythrocyte values were quite uniform within a narrow range of variation, while the hemoglobin content was comparatively irregular within a wider range of variation. The major changes in the levels of mean values of both the red cells and the hemoglobin, however, were found to be statistically significant. The directions or trends in the levels of the erythrocyte and hemoglobin mean values did not necessarily move in opposite directions. The general levels of the erythrocyte and hemoglobin mean values were not identical for two consecutive years, those of 1927-1928 being higher than those of 1928-1929. The fluctuations of both red cell and hemoglobin mean values observed in one group of animals were also usually observed in another group examined during the same months.

Consecutive weekly observations on the total white cell count of the peripheral blood were made on five groups of normal rabbits, a total of forty-five animals, during a period of twenty months from October, 1927, to July, 1929. The duration of individual group examinations varied from eight to thirty-five weeks. In the case of four groups followed thirteen to thirty-five weeks, the general trend of the total white cell means was toward increasing values, with the group followed eight weeks, the means were maintained at a constant level. The changes in the levels of the granular cell means were usually accompanied by changes in a similar direction of the nongranular cell means. In the case of three of the four groups followed for the longest periods, the greatest relative alterations occurred in the nongranular cells. The fluctuations in the mean values of the total white cells and of the granular and the nongranular cells that were observed in one group of rabbits were also generally observed in another group examined during the same months. The period of greatest irregularity in the mean values of the total white cell means, and of the granular and the nongranular cell means as well, occurred during the late winter and spring months of both years. The general level of the total mean values of the white cells in the groups examined during 1927-1928 was higher than that of the groups observed during 1928-1929. A similar difference was found in the granular and nongranular mean values but it was somewhat less marked in the case of the granular cells.

AUTHORS' SUMMARIES

THE RELATION OF HEPATITIS TO CHRONIC CHOLECYSTITIS II KOSTER, M. A. GOLDZIEHER and W. S. COLLENS, Surg. Gynec. Obst. **50** 959, 1930

Sections of the liver, taken not less than 8 cm. from diseased gallbladders, in twenty-five of twenty-seven patients, showed chronic inflammatory changes, mainly in the connective tissue about the larger intrahepatic branches of the portal vein. A few nodules of perivascular infiltration were scattered through the liver tissue. The lesion of the gallbladder is regarded as the prior lesion.

RICHARD A. LIFVENDAHN

SOLITARY TUBERCLE OF THE BLADDER J. A. BOWEN and G. A. BENNETT,
Surg. Gynec. Obst. **50** 1015, 1930

There was a lesion of the fundus of the urinary bladder characterized by marked thickening as the result of dense white tissue bands extending from the submucosa into the muscularis and the adjacent fat. Microscopically, the structure was typically tuberculous and contained acid-fast rods. The inner surface was extensively ulcerated, and cystoscopically the condition was regarded as carcinomatous.

RICHARD A. LIFVENDAHN

ARTERIOVENOUS COMMUNICATION BETWEEN RIGHT CORONARY ARTERY AND CORONARY SINUS B HALPERT, *Heart* **15** 129, 1930

In the body of a man, aged 54, who died from a carcinoma of the stomach, an anastomosis between the right coronary artery and coronary sinus was found. During life, there had been a systolic murmur at the apex of the heart, the blood pressure had been 125 systolic and 70 diastolic. The right coronary artery was 22 cm long and from 1.5 to 2 cm in diameter. The anastomosing loop had a structure that was intermediate between an artery and a vein.

GEORGE RUKSTINAT

PARADOXICAL EMBOLISM T THOMPSON and W EVANS, *Quart J Med* **23** 135, 1930

Emboli arising in the systemic venous circulation and lodging in the systemic arterial circulation are known as "paradoxical" or "crossed" emboli. The emboli cross from the venous to the arterial circulation through a patent foramen ovale. The number of recorded cases is not great, and the condition has been recognized only since 1876, when Cohnheim first discovered embolism of the middle cerebral artery arising from the veins of the lower extremities. The authors give a historical review and then classify paradoxical embolism into three groups.

In the first group are those in which thrombosis of the systemic vein is the cause of the embolism, they cite four cases from their own experience, in two of which pulmonary embolism also occurred. It is interesting to note that in one of these cases the patient recovered from cross embolism to the brain.

In the second group are tumor emboli, which are very rare. The authors point out that the possibility of the embolus having traversed the pulmonary circulation before reaching the arterial circulation must be excluded. Thus, they caution that if a growth is present in the lung, even in the presence of a patent foramen ovale, great care must be taken to exclude the possibility of the tumor embolus having traversed the pulmonary circulation. Also, secondary growth deposits in the lung must be excluded by microscopic examination. The suspected tumor embolus should lie free within the lumen of the artery. If it is intimately associated with the wall of the vessel, its formation has probably resulted from the gradual proliferation of tumor cells previously deposited on the intima of the vessel, such observations favor the view that the neoplastic cells have arrived there through the pulmonary circulation. When the embolus is found in the middle cerebral artery, the presence of other deposits in the cerebral cortex suggests that the cells have traversed the pulmonary circulation. When a tumor embolus of the paradoxical type is situated in the cerebral vessels, the clinical notes should contain a history of the sudden onset of a grave symptom such as hemiplegia. When a patent foramen ovale is protected by a valvular fold, the tumor embolus of the paradoxical type can result only following a primary infiltration of the growth along the intra-auricular wall in the right auricle and, finally, its direct extension through the foramen. One authentic case of crossed tumor embolism is reported, the origin of which was in a malignant teratoma of the testicle.

In the third group are the septic emboli, these are the most difficult to account for or to establish as being paradoxical. Because of the facility with which infection passes through the pulmonary circulation, the proof of paradoxical embolism is difficult to establish, even in the presence of an unprotected foramen. It is interesting to note that the foramen ovale is open in about 35 per cent of cases, large enough to admit a small probe in 29 per cent and patent to a pencil in about 6 per cent. The relation between the paradoxical and pulmonary embolus is important since many of the cases are preceded by pulmonary embolism, and the explanation of the subsequent paradoxical embolus is that the blockage in the pulmonary artery raises the intracardiac pressure on the right side, thus the foramen ovale is forced open. Then the second embolus, which reaches the heart, is carried through this foramen, if its size permits. To establish paradoxical embolism by an increase in the pressure in the right auricle, it is necessary that over one third of the pulmonary circulation be obstructed.

N ENZER

PERIOSTEAL NEUROFIBROMATOSIS, WITH A SHORT CONSIDERATION OF THE
WHOLE SUBJECT OF NEUROFIBROMATOSIS F PARKES WEBER, Quart J
Med **23** 151, 1930

The main point in this review is to establish that many of the changes in the bones in neurofibromatosis, if not all, are due to periosteal neurofibromas and not to primary involvement of the bone. Brooks and Lehman, in 1924, studied the changes in the bone in seven cases of neurofibromatosis and showed the presence of neurofibromatous involvement of the periosteum, which seemed in some instances to have penetrated the bone and in all instances to have produced gross changes in the outline of the diseased bone. Weber describes a much thickened and curved tibia in a case of neurofibromatosis in which the periosteal thickening was due to diffuse neurofibromatous infiltration. But he feels that many of the changes in the bone previously reported as being the result or the complication of neurofibromatosis, and generally explained as being the result of elephantiasis, are really secondary to the actual involvement of the periosteum. This periosteal involvement serves as a stimulus to the growth of the bone, and, hence, explains many of the cases of increase in the length of a single long bone.

N ENZER

THE MAIN BRANCHES OF THE CORONARY ARTERIES IN ACUTE RHEUMATIC
CARDITIS C B PERRY, Quart J Med **23** 241, 1930

Severe intimal thickening in the main branches of the coronary arteries was discovered in a child, who had suffered from typical anginal pain, and had died during an attack of acute rheumatic fever carditis. This discovery stimulated the author to search for a similar involvement of the coronary artery in other cases of rheumatic fever carditis. Nine hearts were examined from patients, under 20 years of age, who died of acute rheumatic carditis. In all of these, changes were noted in the main branches of the coronary arteries. The changes were patchy thickening of the intima and focal lymphocytic infiltration. The internal elastic layer was irregular, occasionally widely spaced and occasionally condensed. Some intimal proliferation was also noted. In the media, the muscle cells were vacuolated. There was loss of some nuclei and patchy cellular infiltration. The adventitia was thickened, also showing lymphocytic infiltration. Deposits of fat in the wall and in the intima were not found. This emphasizes the widespread involvement of the vascular system in cases of rheumatic fever and emphasizes the importance of a careful search for lesions in the coronary system.

N ENZER

CRUVEILHIER-BAUMGARTEN'S SYNDROME (CIRRHOSIS) SERBAN BRATIANO, N
VISINEANO and E SOLOMON, Ann d'anat path **6** 293, 1929

From an anatomic point of view, this syndrome is characterized by an enormous splenomegaly, by a chronic lesion of the liver (progressive "functional" atrophy, congenital hypoplasia and cirrhosis) and, what is pathognomonic, by the presence, in the falciform ligament, of a large venous channel leading to a communication between the portal and the parieto-abdominal circulations. This venous channel is regarded as an obliterated and dilated umbilical vein, or possibly a dilated para-umbilical vein. Histologically, the spleen shows changes that are due to stasis.

Clinically, there is a primary splenomegaly and signs of a portal "hypertension" evidenced by the development of an accessory thoraco-abdominal circulation forming enormous unilateral varices. The disease is probably congenital. The authors report a personal observation and give in detail a clinical and pathologic summary of the syndrome.

B M FRIED

TWO CASES OF DIFFUSE PHLEGMONS OF THE STOMACH D PETIT-DUTAILLIS,
I BERTRAND, BOPPE and WAITZ, *Ann d'anat path* 6 391, 1929

A report of two cases of phlegmonous gastritis is given in detail. The pathologic process, according to the authors, is always at its maximum at the level of the pylorus. The infiltration stops abruptly at the cardia and the pylorus, never involving the duodenum or the esophagus. The pus infiltrates the submucosa, pushing apart the muscularis mucosae and the muscularis, thus forming a dissecting phlegmon. The mucosa shows edema and a lymphocytic infiltration, the muscularis shows a discrete area of pus. There is a lymphangitis in the subserous membrane where thrombosed vessels are conspicuous. There has been a generalized peritonitis in 70 per cent of the published cases. It is interesting that a diffuse gastric phlegmon may follow a gastrectomy or a gastro-enterostomy.

B M FRIED

A HISTOLOGIC STUDY OF ACUTE CARDIAC RHEUMATISM H DARRE and G
ALBOT, *Ann d'anat path* 6 465, 1929

The lesion caused by acute rheumatic disease shows nothing characteristic in tissues that are rich in collagen. On the contrary, in areas with a reticular structure and also in those that are rich in lymph spaces, the acute condition tends to form nodular structures resembling those described by Aschoff in the myocardium.

B M FRIED

OCULAR COMPLICATIONS OF PALUDISM H VILLARD, *Arch d'opht* 47 200, 1930

The conjunctiva is affected in cachectic forms of paludism, becoming dry and wrinkled. In the acute stage of malaria, ulceration and superficial keratitis are seen. Deep keratitis and iritis are more rare. The vitreous may show hemorrhages and exudation. Inflammations of the choroid are not usually seen with the ophthalmoscope, but have been found in eyes examined post mortem. Spasm, hyperemia and hemorrhage of the vessels of the retina and retrobulbar optic neuritis may occur. Optic atrophy is never seen in the early stages of malaria, it is always the outcome of optic neuritis in its grave form. The frontal ramus of the ophthalmic branch of the trigeminal nerve is often affected by neuritis. Severe ocular motor paralyses have also been described in districts in which malaria is endemic and severe.

CHARLES WEISS

A KNOTTED PULMONARY EMBOLUS NIPPE, *Deutsche Ztschr f gerichtl Med*
15 330, 1930

The embolus originated in the right femoral vein following an operation for gangrenous appendicitis. An end of the embolus projected into the right auricle and the unique knot is ascribed to the action of the currents in the auricle.

HIRSCHSPRUNG'S DISEASE K OGAWA, *Frankfurt Ztschr f Path* 40 26, 1930

A case of Hirschsprung's disease is reported. The infant, aged 2 months, had been constipated since birth. Bowel movements were obtained only by the use of enemas. At autopsy, the large intestines were markedly dilated and their walls hypertrophic. The mesentery was of normal length and showed no scar tissue. Histologically, all the elements of the wall of the intestines were hypertrophic, with the exception of the nervous elements, in particular the plexus of Auerbach. The author assumes that the marked meteorism of this case was due to the fact that the peristalsis, even though of normal intensity, was too weak for the markedly hypertrophic colon. The belief is expressed that cases of megacolon which show neither meteorism nor any other clinical signs of Hirschsprung's disease reveal, in addition to hypertrophy of the muscle fibers of the intestine, abnormally large nervous elements in the intestinal wall. The peristaltic wave, therefore, might be more powerful, lead to normal bowel movements and prevent the appearance of the clinical symptoms of Hirschsprung's disease.

ARTERIOSCLEROSIS IN THE PARROT G PALLASKE, Frankfurt Ztschr f Path
40 64, 1930

The arteriosclerotic changes in two parrots, about 30 and 40 years old, are described. The conclusion is reached that arteriosclerotic lesions in the parrot correspond with arteriosclerotic changes in man, but not with those in the dog and the horse.

HODGKIN'S DISEASE COMBINED WITH ACUTE MYELOID LEUKEMIA M A
SKWORZOFF, Frankfurt Ztschr f Path 40 81, 1930

The lymph nodes in a girl, aged 8, especially those in the region of the neck, were markedly enlarged and showed changes typical of Hodgkin's disease. Dorothy Reed cells and many eosinophils were encountered. A fibrous replacement of the lymph nodes was also noted. In addition, there were many polymorphonuclear leukocytes, myelocytes and myeloblasts. The latter gave a positive oxydase reaction. The spleen and bone-marrow were the seat of myeloid metaplasia. Accumulations of myeloid cells were present in the liver, suprarenal glands, uterus, ovaries, urinary bladder and kidneys. Chemical examination of the blood showed 360,000 white cells, the differential count revealed myeloblasts, 85.5 per cent, promyelocytes, 2 per cent, myelocytes, 1.5 per cent, metamyelocytes, 3 per cent, neutrophils, 4 per cent, lymphocytes, 2 per cent, monocytes, 0.5 per cent, and eosinophils, 1.5 per cent, thus the blood picture was characteristic of myelogenous leukemia. A gangrenous process of the pharynx aided in making the diagnosis. The question is discussed whether this case presents a true myelogenous leukemia superimposed on a primary Hodgkin's disease, or whether this is a case of a leukemia-like reaction of the organism against the unknown virus of Hodgkin's disease.

ENCEPHALITIS IN EXSICCOSIS M A GOLDZIEHER, Klin Wchnschr 9 981, 1930

A proliferative process in the midbrain is described which is regarded as having significance in water metabolism.

CHARACTERISTICS OF BILIRUBIN IN ICTERUS NEONATORUM L ASCHOFF and
R HUMMEL, Virchows Arch f path Anat 275 1, 1930

In the opening article of a volume of *Virchows Archiv* issued as a Festschrift to its editor, Lubarsch, on the occasion of his seventieth birthday, Aschoff and Hummel discuss some of the peculiarities of bilirubin in icterus neonatorum. In agreement with most modern writers, they hold that icterus neonatorum is a physiologic process that is to be distinguished from pathologic icterus of the newborn or icterus neonatorum. One of the most striking characteristics of the physiologic jaundice is the crystallization of bilirubin in the living condition, a phenomenon to which Orth called attention more than fifty years ago. According to the present writers, this phenomenon does not occur in the jaundice of later life except in the rarest instances, and then only in the form of icterus that Aschoff has termed hyperfunctional and not in the obstructive type. In icterus neonatorum, crystallization of bilirubin is seen not only in the blood, but also in the tissues, especially within fat cells, and in the fluid of the serous cavities. Crystallization was noted most frequently, and the content of bilirubin was highest in the pericardial cavity, next in the peritoneal cavity, then in the subdural space and least in the pleural cavities. This variation in the content of the bilirubin in the serous fluids is directly proportional to the richness of the lining serous membrane in histiocytes. The crystals of bilirubin seen in the fluids were usually within free histiocytes. In premature infants, in stillborn fetuses and in new-born infants immediately after birth, the blood, the serous fluids that contain bilirubin, the bile of the gallbladder and the meconium give only the indirect van den Bergh reaction. The direct van den Bergh reaction, which Aschoff previously ascribed to bilirubin that has passed the liver cell, does not appear until the liver function has been established. Deposits of biliary pigment were not seen

in the urine of icteric new-born infants The kidney does not appear to be able to excrete the form of bilirubin that is present in icterus neonatorum, and the tubular bilirubin infarcts sometimes seen in the kidneys of these infants are not due to excretion of the pigment The peculiar characteristics of the bilirubin of icterus neonatorum are interpreted as evidence of excessive extrahepatic formation of bilirubin in the fetus and in the new-born infant

O T SCHULTZ

THE ALVEOLAR PHAGOCYTES OF THE LUNG F J LANG, *Virchows Arch f path Anat* **275** 104, 1930

In a previously reported work on tissue culture of the lung, Lang reached the conclusion that the phagocytic cells of the lung alveoli are mesenchymal in origin and are not alveolar epithelia In the present article, he briefly summarizes his work and that of others that upholds this conclusion The article includes material on the embryologic investigations of Policard, Ogawa, and Chiodi, his own work on tissue culture, the morphology of the cells and their presence within the septums, the results of the application of the supravital staining technic by Gardner and Smith and by Foot, a description of the ability of the cells to phagocytose bacteria and particulate matter and the storage of lipid by the cells in lipid histiocytosis, as reported by Bloom All these facts, according to Lang, establish beyond question the nonepithelial character of the alveolar phagocytes, or septum cells, as he prefers to term them The cells are the derivatives of the system of slumbering mesenchymal cells that retain their embryonic potencies of being awakened into activity under a variety of stimuli In the lung, their function is the cleansing of the lung of foreign particles that reach the normal lung tissue, and the protection of the lung in disease by the ingestion of bacteria, particulate material and colloid substances that reach the lung from without or by way of the blood stream

O T SCHULTZ

BASOPHIL CELLS OF THE HYPOPHYSIS AND CHRONIC RENAL DISEASE W BERBLINGER, *Virchows Arch f path Anat* **275** 230, 1930

Berblinger investigated variations in the content of basophil cells in cases of adenohypophysis in a series of seventy-one adults of both sexes without renal disease, and in a series of seventy-one adults of both sexes with chronic renal disease In the group without renal disease, the basophil cells were increased above what Berblinger considered the normal average in 28 per cent, and decreased in 11 per cent In the group with renal disease, the number of basophil cells was increased in 67 per cent, and decreased in 3 per cent The numerical variations bore no relation to the age or to the constitutional type Berblinger concluded that the frequency with which the basophil cells are increased in number in cases of renal disease indicates a relationship between this type of cell, the blood pressure and the renal function

O T SCHULTZ

MULTINUCLEATED SPERMATIDS IN THE TESTIS W DI BIASI, *Virchows Arch f path Anat* **275** 250, 1930

Multinucleated spermatids were seen in the testes of 27 per cent of 165 cases examined In a series of 80 cases more carefully examined, they were detected in 58 per cent They are about the size of spermatocytes, but may appear as multinucleated giant cells They are formed by fusion, although repeated nuclear division without division of the cells cannot be excluded as a mode of formation They were seen at all ages after puberty They occur in testes that have been only slightly damaged by the general state of the person, and are probably also a constituent of the normal testis

O T SCHULTZ

BONE-MARROW OF THE FEMUR T FAHR, *Virehows Arch f path Anat* **275**
288, 1930

Fahr presents a study of the bone-marrow of the femur, based on 500 necropsies in which the entire femur was removed and the marrow examined. The age in 13 cases, including those for control and for comparison, was under 18 years. Fahr agrees with Askanazy, Hedinger and Neumann in their assertion that the usual statement in textbooks that the normal marrow of the long bones in adults is entirely fatty is incorrect. In his series, an adipose marrow, which sometimes contained a few small islands of red marrow at the upper end of the diaphysis, was seen in only 14 per cent. In 60 cases of tuberculosis, the marrow was wholly fatty in only 3 per cent, considerably under the average for the group. In syphilis, the marrow was fatty in 38 per cent, a figure much above the average for the group, and in infectious diseases other than tuberculosis or syphilis, the figure was 16 per cent. Contrary to the opinion of Schridde, mucoid degeneration of the marrow was not associated with increasing age, but it was encountered more frequently in persons under 50 years of age than in those above this age. It was seen in 12 per cent of the cases of tuberculosis, as compared with 8 per cent for the rest of the series. A practically complete replacement of adipose by red marrow was noted in 7 per cent of the 487 persons over 18 years of age. Such complete replacement was seen in 24 per cent of 55 cases of tuberculosis in persons over 18 years of age, as compared with 5 per cent for the rest of the group. Replacement of adipose by red marrow in cases of tuberculosis may be as marked as in pernicious anemia. The change is not due to actual tuberculous involvement of the marrow, but to a disturbance of leukopoiesis. The nature or cause of this disturbance is not discussed. That there is also slight disturbance of erythropoiesis in tuberculosis is evidenced by the presence of iron pigment in the Kupffer cells of the liver. Fahr presents tabulations of the distribution of iron in the liver, spleen and celiac lymph nodes in tuberculosis and pernicious anemia.

O T SCHULTZ

THE CYTOLOGY OF THE CONJUNCTIVA IN TRACHOMA AND THE PROBLEM OF ITS
PATHOGENESIS P P DWYKOFF and E F LEUKOWICZ, *Ztschr f Augenh*
71 314, 1930

In trachoma, the cytology of the material obtained by expression of follicles and scrapings of the conjunctiva is characteristic of the disease and is related to the clinical picture. In stage 1, the lymphoid type of cells predominate, especially the small lymphocytes. The most characteristic and pathognomonic cells seen are the lymphoblasts. Plasma cells are rarely seen, and there are few polymorphonuclears or eosinophils. Epithelial cells are present in large masses. In stage 2 there is a general increase in all of the cells, particularly in the large lymphocytes and lymphoblasts. There is also a slight increase in the plasma cells. Nucleated red cells now make their appearance. Stage 3 is characterized by a decrease in the lymphoblasts, lymphocytes and plasma cells. This picture is not seen in allied diseases of the conjunctiva, such as follicular, hyperplastic, swimming pool and Parinaud's conjunctivitis, or in tuberculosis.

The authors emphasize the point that the cells of the trachomatous follicle, which writers (Lohlein, and others) have called epithelioid, are really lymphoblasts. They agree with Pasaheft that the conjunctiva is a blood-forming, lymphatic apparatus, and conclude that the proliferation of young cells of the lymphoid series, especially lymphoblasts, and the absence of morphologic signs of inflammation support the idea that trachoma is not an inflammatory but a hyperplastic process similar to leukemia.

CHARLES WEISS

Microbiology and Parasitology

RECURRENT AGRANULOCYTOSIS B H RUTLEDGE, O C HANSEN-PRUSS and W S THAYER, Bull Johns Hopkins Hosp 46 369, 1930

We are presenting a remarkable instance of cyclic, agranulocytic angina associated with fever and constitutional symptoms but without anemia, beginning at the age of 2½ months and recurring at intervals of approximately three weeks, during the entire life of a man 20 years of age. While apparently unique in medical literature, the picture is so sharply defined and clear that we are inclined to think that it represents a definite complex of symptoms which may be less infrequent than one might fancy at the moment. For this reason, we desire to place the history on record.

AUTHORS' SUMMARY

THE HYDROLYSIS OF SODIUM HIPPURATE BY VARIOUS BACTERIA ISABELLE GILBERT and MARTIN FROBISHER, JR., Bull Johns Hopkins Hosp 47 55, 1930

Except *Bacillus aerogenes* and *B. bronchisepticus*, the gram-negative, aerobic, nonspore-forming rods studied were without action on sodium hippurate. Staphylococci generally split up the hippurate, but the power varies in different strains. The results indicate that the test will be of value.

THE UPPER RESPIRATORY FLORA OF INFANTS YALE KNEELAND, JR., J. Exper. Med 51 617, 1930

The upper respiratory tract is sterile at birth. In the first two weeks of life the infant acquires a basal flora comparable to that of adults except that the potential pathogens are absent. During the ensuing months the potential pathogens may appear without giving rise to symptoms and by eight months the infant's flora is entirely comparable to the adult's. There is no evidence of a specific bacterial incitant for the first colds of infancy. In infants with recurrent colds, secondary infection of the nose with pneumococci or *B. Pfeifferi* probably plays a part.

AUTHOR'S SUMMARY

THE TRANSMISSION OF YELLOW FEVER NELSON C DAVIS, J. Exper. Med 51 703, 1930

Samur sciuens has been infected with yellow fever virus, both by the inoculation of infectious blood and by the bites of infective mosquitoes. Some of the monkeys have died, showing lesions, including hepatic necrosis, suggesting yellow fever as seen in human beings and in rhesus monkeys. Virus has been transferred back to *M. rhesus* from infected *Samur* both by blood inoculation and by mosquito bites. The virus undoubtedly has been maintained through four direct passages in *Samur*. Reinoculations of infectious material into recovered monkeys have not given rise to invasion of the blood stream by virus. Serums from recovered animals have protected *M. rhesus* against the inoculation of virus. It has been possible to pass the virus to and from *Ateles ater* by the injection of blood or liver and by the bites of mosquitoes. The livers from two infected animals have shown no necrosis. The serum from one recovered monkey proved to be protective for *M. rhesus*. Only three of twelve *Lagothrix lagotricha* have reacted to yellow fever virus by a rise in temperature. Probably none has died as a result of the infection. In only one instance has the virus been transferred back to *M. rhesus*. The serums of recovered animals have had a protective action against yellow fever virus.

AUTHOR'S SUMMARY

EXPERIMENTAL EPIDEMIOLOGY OF TUBERCULOSIS MAX B LURIE, J. Exper. Med 51 729, 743, 753 and 769, 1930

If normal guinea-pigs are confined with an equal number of tuberculous cage mates the incidence of "contact" tuberculosis is increased by crowding. This is

probably due largely to an increase in the amount of tubercle bacilli available in the more crowded cages, although no constant relationship could be established between the intensity of the exposure and the incidence of tuberculosis acquired by contagion. Other factors must be determined. If guinea-pigs are inoculated intraperitoneally with a given quantity of human tubercle bacilli and distributed in different degrees of crowding, the duration of survival is shortened in the more crowded animals and the incidence of chronic types of tuberculosis is greater among the less crowded animals.

Guinea-pigs living in the same room but not in the same cage with tuberculous animals acquire tuberculosis, characterized by a chronic course, a marked involvement of the lungs, often with cavity formation, and a massive tuberculosis of the tracheobronchial nodes, the mesenteric and cervical nodes are slightly or not at all affected. The route of infection in these guinea-pigs is almost always the respiratory tract. Of 103 guinea-pigs exposed for a period of up to thirty-two months 15, or 14.5 per cent, developed tuberculosis. The shortest period of exposure leading to fatal tuberculosis was eight months. The incidence of this tuberculosis acquired by air-borne contagion increases with the duration and intensity of the exposure up to a certain point. A large percentage of the guinea-pigs weathered a continuous exposure to the tubercle bacillus for thirty-two months without becoming tuberculous. This may be due to an innate natural resistance against tuberculosis, or to an acquired immunity resulting from the continuous exposure to the contagion.

If normal guinea-pigs are confined with tuberculous cage mates in cages where the food becomes contaminated with the excreta, laden with tubercle bacilli, of the inoculated animals, the incidence of acquired tuberculosis among them is greater than among guinea-pigs similarly exposed in cages where this mode of infection is largely eliminated. The disease acquired in the first type of cage is largely of enteric origin and is chronic in type. The disease acquired in the second type of cage is of respiratory origin and has a more acute course.

In tuberculosis of guinea-pigs acquired by contact with tuberculous guinea-pigs under conditions permitting the entrance of tubercle bacilli by way of both the alimentary and the respiratory tracts, the type of lesion produced depends on the relative intensity of exposure to infection by one or the other channels. With the gradual elimination of exposure to alimentary infection tuberculosis is more and more completely engrafted through the respiratory route. With the gradual increase in the intensity of exposure to alimentary infection, the disease becomes more and more completely enteric in origin. Some evidence is presented that the engrafting of tuberculosis by way of the alimentary route inhibits the development of respiratory disease.

AUTHOR'S SUMMARIES

EXPERIMENTS WITH THE VIRUS OF POLIOMYELITIS RICHARD THOMPSON, J. Exper. Med. **51** 777, 1930

Efforts to adapt the virus of poliomyelitis to the rabbit organism and to produce poliomyelitis in rabbits by testicular injection and by cerebral injection after testicular passage produced no evidence that the virus could be adapted in this manner. Suggestive symptoms produced in very young rabbits were duplicated in nonspecifically treated and in uninoculated controls. The admixture of a vaccine virus, adapted to the rabbit organism, with the poliomyelitis virus in similar injections and passages did not aid the adaptation. The virus of poliomyelitis did not survive twenty-four hours in the rabbit testicle—whether alone or mixed with vaccine virus. Repeated intraperitoneal and intradermal injection of poliomyelitis virus and of poliomyelitis and vaccinia virus mixtures produced no disease in rabbits. Massive doses of concentrated virus by stomach tube in conjunction with meningeal irritation produced no symptoms in rabbits. No neutralizing substances against poliomyelitis virus could be produced in rabbits by the repeated intraperitoneal and intradermal injection of poliomyelitis virus or of poliomyelitis-vaccinia virus mixtures. Although attempts to infect monkeys by intrastomachic injections, after

bile irritation of the mucosa, were entirely negative, evidence was obtained that repeated intrastomachic injection after bile irritation may produce an appreciable degree of immunity. No evidence could be obtained that the cellular elements of the blood contain the virus in any greater proportion than the whole blood. One attempt to immunize by neutral virus-serum mixtures was entirely negative.

AUTHOR'S SUMMARY

METHODS FOR THE PURE CULTURE OF CERTAIN PROTOZOA R. W. GLASER and N. A. CORIA, *J. Exper. Med.* **51** 787, 1930

Some mediums are described which inhibit bacterial growth, but are favorable to protozoan development. A purification technique, which takes advantage of geotropic responses, was devised and used successfully with seven species of protozoa, including flagellates and ciliates. The method was also used with *Spinillum*. For one flagellate which could not be purified in this manner, a procedure involving chemical sterilization was employed. *Paramecium caudatum* was purified, but failed to develop subsequently in the absence of living micro-organisms. Four of the protozoa which were purified ingest other micro-organisms normally. The work shows that purified protozoa grow well under proper conditions, and then they can be studied culturally and biologically, like bacteria.

AUTHORS' SUMMARY

DISSOCIATION OF THE TUBERCLE BACILLUS S. A. PETROFF and WILLIAM STEENKEN, JR., *J. Exper. Med.* **51** 831, 1930

Petroff and Steenken, in studying the colony formation of the tubercle bacillus, found evidences of dissociation similar to that of other organisms. They distinguish several types of colonies but have studied only the two extreme types, the "R" and "S". They use the term "R" to indicate greater resistance to environment and relative avirulence, and "S" to indicate greater sensitiveness to environment and more virulence to certain species. The terms rough and smooth can be applied only to the avian bacillus when grown on plain gentian violet-egg medium. The addition of 0.25 per cent of sodium taurocholate to this brings out the "R" and "S" types. The human tubercle bacillus has been dissociated with great difficulty, and the study is not yet complete. The "R" and "S" types have been obtained from four BCG cultures, this work has been reported elsewhere. The authors believe that each organism has two components, "R" and "S". If the environment is favorable, "R" may change to "S," or vice versa.

L. E. COOLEY

STUDIES ON MEXICAN TYPHUS FEVER HANS ZINSSER and ALBERT P. BATCHELDER, *J. Exper. Med.* **51** 847, 1930

The authors reinvestigated some of the fundamental problems of Mexican typhus fever. They found that the virus is not filtrable. The results of the filtration experiments suggest that the virus is comparable in magnitude to the tunica bodies observed by Mooser. The virus is firmly associated with red blood cells, but hardly at all with leukocytes. The virus remains alive in tunica material and in glass capsules within the peritoneum of guinea-pigs for about ten days. They failed to keep the virus living except in the presence of living cells. Tunica material containing Mooser bodies (probably *Rickettsia*) is more virulent than blood plasma. The authors believe that the tunica lesions in guinea-pigs are an integral part of the disease. Convalescent blood and virus mixed in a test tube afford protection if the blood is taken between the first and tenth days after defervescence. Several guinea-pigs developed an active immunity by this method. No complement-fixation bodies were found. There was suggestive evidence of an active immunization with tunica material in formaldehyde. The authors believe that the small giemsa-staining bodies observed by Mooser in the tunica of guinea-pigs with Mexican typhus represent the virus of the disease.

L. E. COOLEY

CENTRIFUGE EXPERIMENTS WITH THE VIRUS OF VACCINIA F F TANG, J
Exper Med **51** 859, 1930

Centrifuge experiments have been carried out with cell-free, active filtrates of vaccinia virus. The experiments have shown that the virus can be concentrated by this method, even in filtrates which have been subjected to prolonged preliminary centrifugalization to throw down any inert particles which may have been present in the original filtrate. This fact, together with the knowledge that the virus can be almost completely held back by the Berkefeld N filter, as reported previously, indicates that the virus may be of considerable size.

AUTHOR'S SUMMARY

CULTIVATION AND CLASSIFICATION OF "BACTEROIDES," "SYMBIONTS," OR
"RICKETTSIAE" OF *BLATTELLA GERMANICA* R W GLASER, J Exper Med
51 903, 1930

In *Blattella germanica*, the German roach or "croton bug," bacterioeytes are found in all individuals of both sexes. These bacterioeytes are scattered throughout the fat tissue and their cytoplasm is filled with micro-organisms. Evidence is presented to show that the intracellular parasites are diphtheroidal bacilli. These diphtheroids are transmitted from one generation to another through the ova. By using a technique previously described, the intracellular parasites were isolated and cultivated from the adult bacterioeytes and from embryos. Two diphtheroidal strains were cultivated with approximately equal frequency. These two strains resemble one another closely enough to be considered a single species but show certain minor differences. The size, general morphology and tinctorial reactions of the two cultures correspond to the intracellular parasites of *Blattella germanica*. They may be distinguished from the three types of *Corynebacterium periplanetae* variety *americana* previously described. For the species here discussed the name *Corynebacterium blattellae*, nov. sp., is proposed.

AUTHOR'S SUMMARY

THE EPIDEMIOLOGY OF SPECIFIC INFECTIOUS CYSTITIS AND PYELONEPHRITIS
OF COWS F S JONES and RALPH B LITTLE, J Exper Med **51** 909, 1930

Bacteriologic examination of the genito-urinary tract of calves originating in a herd in which infectious cystitis and pyelonephritis existed among the cows revealed a variety of cultural types of diphtheroids. Of these types, one obtained from a considerable number of the calves resembled in morphology and cultural characteristics the organism cultivated from the actual cases of the disease. This group had agglutination affinities like those of the organism mentioned and was capable of absorbing agglutinin from antiserum specific for it. When three cows were inoculated intra-urethrally with cultures isolated from the sheaths of calves, two developed transient infections and the other a severe prolonged cystitis and pyelonephritis.

AUTHORS' SUMMARY

THE EFFECT OF CATHODE RAYS UPON CERTAIN BACTERIA RALPH W G
WYCKOFF and THOMAS M RIVERS, J Exper Med **51** 921, 1930

For the two motile bacilli, *B. coli* and *B. aertryke*, the absorption of a single 155 kilovolt electron is sufficient to cause death. Furthermore, all, or nearly all, the electrons absorbed are lethal. The same is undoubtedly true of *Staphylococcus aureus*. In addition to providing a quantitative picture of the interaction of bacteria and cathode rays, these results suggest that radiation of the energy content used in our experiments is not suitable for altering the inheritable characteristics of bacteria. The differences in sensitivity to cathode rays shown by the bacteria studied can be explained by the purely physical factor of size. Counts giving significant conclusions concerning killing rates can be obtained only if there is no clumping of the cells when spread and only if the cells are not allowed to

multiply before irradiation Both these precautions seem rarely to have been met in the experiments with roentgen rays and with other forms of radiation that have been made in the past

AUTHORS' SUMMARY

RISE IN TEMPERATURE PRECEDING THE SYMPTOMS IN EXPERIMENTAL POLIO-MYELITIS S D KRAMER, K H HENDRIE and W L AYCOCK, J Exper Med **51** 933, 1930

The data presented in this paper offer a means of earlier recognition of experimental poliomyelitis in the monkey The early appearance of the temperature rise (one to three days before the onset of the usual recognizable symptoms) associated with spinal fluid changes suggests that there is a stage in the experimental disease corresponding to preparalytic human poliomyelitis

AUTHORS' SUMMARY

INFECTIOUS MYXOMATOSIS OF RABBITS T M RIVERS, J Exper Med **51** 965, 1930

The virus of infectious myxomatosis of rabbits (*Sanarelli*) induces multiple lesions in the skin, lymph glands, tunica vaginalis, epididymis, testicle, spleen and lungs Growth and destruction of cells in the epidermis overlying the myxomatous masses lead to the formation of vesicles Cytoplasmic inclusions are found in affected epidermal cells Occasionally, similar inclusions are seen in other involved epithelial cells The nature of the inclusions is an open question In the myxomatous masses situated in the subcutaneous and other tissues, evidences of alteration and growth of certain cells are observed

AUTHOR'S SUMMARY

THE SURVIVAL OF YELLOW FEVER VIRUS IN CULTURES PAUL A LEWIS, J Exper Med **52** 113, 1930

The virus of yellow fever has been found to survive in artificial culture mediums for at least twelve days at a temperature of 35 C No visible growth has been present and no reproduction of the virus has been demonstrated Infections have been obtained in rhesus monkeys with two strains of virus in quantities as small as 0.00001 cc of infectious blood, and with one strain in an amount probably as minute as 0.000001 cc

AUTHOR'S SUMMARY

BARTONELLA MURIS ANEMIA IN ALBINO RATS J MARMORSTON-GOTTESMAN and DAVID PERLA, J Exper Med **52** 121 and 131, 1930

The virus of *Bartonella muris* anemia of splenectomized rats may be transmitted to normal young unoperated rats and rabbits This confirms the observations of Ford and Eliot *Trypanosoma lewisi* infections in normal adult rats are accompanied by an anemia most marked at the height of the infection and the appearance of *Bartonella muris* bodies in the red blood cells In young rats *Trypanosoma lewisi* may produce death from the severity of the anemia, complicating the disease The anemic virus may be separated from *Trypanosoma lewisi* infected blood by passage through young rabbits with subsequent maintenance of the strain in immature rats A strain of the virus of *Bartonella muris* anemia capable of producing anemia in young rabbits and young rats for successive transfers has been isolated from the blood of normal adult unoperated rats by passage through young rabbits The adult normal rat is a carrier of the *Bartonella muris* virus Splenectomy in young suckling rats separated from the mother is not followed by a *Bartonella muris* anemia The young suckling rat is not a carrier of the infection

Autoplastic splenic transplants were made in adult albino rats four and seven weeks prior to splenectomy and the protective effects against infection with the *Bartonella muris* anemia observed One fourth of the spleen left in situ will protect adult albino rats against *Bartonella muris* anemia Autotransplantation of splenic

tissue in adult rats is successful in over 90 per cent of instances. Autoplastic splenic transplants performed seven weeks prior to splenectomy afford protection against *Bartonella muris* anemia in more than 50 per cent of instances, whereas four week old transplants do not protect. A comparative histologic study of the transplants of protected and unprotected rats reveals a regeneration of the pulp cells in the protected rats and an exhaustion destruction of the pulp in the unprotected rats. The reticular cells play a specific rôle in protecting the adult albino rat against *Bartonella muris* anemia.

AUTHORS' SUMMARIES

FURTHER NOTES ON THE CULTURE OF THE NITROSO-BACTERIUM H. S. FREMLIN, J. Hyg. 29 236, 1929

The nitrosobacterium inoculated into sterile urine does not produce nitrites. If, however, urine is added to an active culture of this micro-organism, nitrites are rapidly developed.

A nitrosobacterium culture developed in bulk in peat and chalk can be used as a urinal. After passing through this urinal, all ammonia in urine appears to have been converted into ammonium nitrite and nitrate. No odor is noticeable when this urine is left to evaporate at either 37 C. or at room temperature.

Urine rendered ammoniacal before use and then sterilized is also a good medium for the growth of the nitrosobacterium.

The nitrosobacterium is difficult to isolate because (1) when colonies are developed on a dilution plate sufficiently spaced to allow of certainty in subculture, nitrification only rarely takes place in the subculture, and when it does take place some months are required for the production of a measurable amount of nitrite, and because (2) the nitrosobacterium usually grows in association with some other, more rapidly growing species. The colonies of this other micro-organism often appear to be pure, but when growth has proceeded for some days individual colonies of the nitrosobacterium may appear in a certain percentage of the plates.

AUTHOR'S SUMMARY

AN EPIDEMIOLOGICAL STUDY OF DIPHTHERIA IN A REMOTE NEW ZEALAND COMMUNITY C. E. HERCUS, R. A. SHORE, H. E. BARRETT and J. H. NORTH, J. Hyg. 29 243, 1929

The epidemiologic and immunologic studies of two outbreaks of diphtheria occurring in a remote and unsettled country district in New Zealand are presented. The first epidemic occurred in August and was thought to be air borne. This was followed in the succeeding spring by the second epidemic, which was probably milk borne.

"The practical lessons which may be learnt from this study are (a) That unless a special buffered diluent is used, the toxin used for Schick testing must be freshly diluted near the place where it is to be used. (b) Active immunization of remote, unsettled communities against diphtheria requires more time, and more intensive courses of prophylactic, than areas where diphtheria has been endemic for some years. (c) In such places with a low original herd immunity, it is essential, even more than in endemic centers, never to omit retesting those who have been inoculated, in order to be certain that any attempt made to induce active immunity to diphtheria may be successful. (d) Estimations of the relative efficiency of diphtheria prophylactics, which are based on the rapidity with which samples of children become immune, are worthless unless all the observations have been made in the same environment on groups having the same original herd immunity. (e) An immunity, good enough to withstand droplet infection in a day school environment may be broken down by massive doses of diphtheria bacilli in milk."

J. N. PATTERSON

PARATYPHOID C, AN ENDEMIC DISEASE IN BRITISH GUIANA GEORGE GIGLIOLI,
J Hyg 29 273, 1929

From seventy-two cases of pyrexial illness occurring in British Guiana, an organism has been isolated which has the cultural and serologic reactions of *Bacillus paratyphosus C* (Hirschfeld). It seems probable that enteric fever due to infection with this organism is now endemic in the colony and is an important cause of sickness and death.

AUTHOR'S SUMMARY

NOTE ON THE CULTIVATION OF AN ACID-FAST BACILLUS FROM LEPROSY
W B WHERRY, J Infect Dis 46 263, 1930

In an attempt to cultivate the bacillus in leprosy, special attention was given to the oxygen and carbon dioxide supply under both aerobic and anaerobic conditions. The medium used consisted of a glycerinated ovomucoid yolk solution added to agar. The best growth was obtained in two tubes kept for a month at partial oxygen tension (little oxygen but carbon dioxide present), after which the tubes were kept under oxygen and carbon dioxide. The rods in the cultures were thinner than tubercle bacilli, and when Löffler's blue was used as a contrast stain they frequently were found to contain one or two blue granules.

THE BEHAVIOR OF ESCHERICHIA COLI AND ITS SPECIFIC BACTERIOPHAGE IN
URINE FRANCES C FRISPEE and WARD J MACNEAL, J Infect Dis 46 405
1930

The colon bacillus grows more actively in human urine when the latter is slightly acid in reaction rather than alkaline.

The bacteriophage actively lytic for the colon bacillus is most effective against this organism in urine culture when the reaction of the latter is acid, with pH of from 5.6 to 6.3.

The bacteriophage is not unfavorably influenced by exclusion of air from the cultures in urine.

The urinary antiseptics, formaldehyde and acriflavine, are distinctly unfavorable to the action of the bacteriophage, in concentrations too weak to exert an appreciable effect on the growth of the colon bacillus in urine.

AUTHORS' SUMMARY

BRUCELLA ABORTUS IN CERTIFIED MILK D E HASLEY, J Infect Dis 46 430,
1930

The results of this investigation show that it is possible to detect *Brucella abortus* in market certified milk by plating methods. *B. abortus* was grown from 10 to 230 samples examined. The 10 positive samples were obtained from 3 of the 5 dairies studied. The highest number of organisms found was 8 per cubic centimeter of milk, the average for the 10 positive samples was 2 per cubic centimeter.

AUTHOR'S SUMMARY

BACTERIOLOGY OF THE BLOOD IN CHRONIC INFECTIOUS ARTHRITIS HARRY M
MARGOLIS and ANNA H E DORSEY, J Infect Dis 46 442, 1930

In several cases of a large series studied, nonhemolytic streptococci were isolated from the blood of patients with chronic infectious arthritis. These streptococci were identical morphologically and culturally with those isolated by us previously from the joint tissues of patients with chronic arthritis.

The infrequency of positive blood cultures in our series as compared with that of Cecil, Nicholls and Stainsby lacks definite explanation. The factors that possibly account for this discrepancy may be extended treatment of the patient before the time of making cultures, the season of the year in which the cultures were taken.

and, most important of all, the inconstancy of the bacteria in the blood of patients with arthritis and the small number of organisms circulating in the blood when bacteremia occurs in arthritis

The occurrence of the organisms in the blood, as well as in the joints of patients with arthritis, suggests that these bacteria are of etiologic significance in this disease

AUTHORS' SUMMARY

LESIONS PRODUCED IN RABBITS BY CULTURES OF *MICROCOCCUS GAZOGENES* (LEWKOWICZ) BEATRICE F HOWITT, J Infect Dis **46** 491, 1930

Lesions of the joints or pyogenic abscesses may be produced in rabbits by intravenous or intraperitoneal inoculations of the mouth organism, *M. gazogenes* (Lewkowicz), a small, gram-negative, gas-producing anaerobe

AUTHOR'S SUMMARY

DIFFERENTIAL ACTION OF OXIDIZING AGENTS ON CERTAIN GRAM-POSITIVE AND GRAM-NEGATIVE ORGANISMS ESTHER WAGNER STEARN and ALLEN E STEARN, J Infect Dis **46** 500, 1930

More than fifty strains of organisms were subjected to various oxidizing environments and their relative susceptibilities tested

A few strains were subjected in the same way to one reducing environment

In general, the gram-negative organisms are more susceptible to an oxidation-reduction environment differing from that of ordinary broth than the gram-positive. This is shown to be true when the oxidation potential is higher, and is indicated in a preliminary way in one case in which the potential is lower, than that of ordinary broth

These results are discussed from the point of view of recent ideas on oxidation-reduction environment

AUTHORS' SUMMARY

THE ABSENCE OF SEASONAL CHANGE IN THE TOXIN-PRODUCING CAPACITY OF THE DIPHTHERIA BACILLUS ARTHUR LOCKE and E R MAIN, J Infect Dis **46** 514, 1930

The toxin production of the Park 8 strain of the diphtheria bacillus has been observed, under controlled conditions, for one year. At no time during that interval was there any indication of a significant seasonal fluctuation in the amount of toxin produced

The seasonal variations in yield occasionally encountered in the large scale preparation of diphtheria toxin may be the result of failure to control completely the composition of the culture medium used, or of failure to use a unit of titration, such as the flocculation unit, which is independent of seasonal fluctuations in animal resistance

AUTHORS' SUMMARY

THE ETIOLOGY OF ERYSIPELAS, ESPECIALLY CHRONIC RELAPSING ERYSIPELAS KARL BAERTHELEIN, Zentralbl f Bakteriologie **114** 271, 1929

In eighteen cases of acute and chronic relapsing erysipelas, diphtheria bacilli and not streptococci were found. Autovaccines prepared from the diphtheria bacilli led to the cure of all but one patient, in whom death occurred too quickly for the vaccine to be used

PAUL R CANNON

THE BEHAVIOR OF HERPES VIRUS IN TISSUE CULTURE E GILDEMEISTER, E HAAGEN and L SCHEELE, Zentralbl f Bakteriologie **114** 309, 1929

The authors succeeded in carrying herpes virus (Basle III) through twenty-two passages in tissue culture, the virus having been absorbed by sterile rabbit testis and grown in a medium consisting of five parts of normal rabbit plasma and one part of spleen extract

PAUL R CANNON

DEVELOPMENTAL STAGES OF THE SYPHILITIC VIRUS IN THE BLOOD E J
ROUKAVISCHNIKOFF, Zentralbl f Bakteriöl **115** 66, 1929

The author kept the blood of syphilitic patients and of animals infected with syphilis for periods of several months and observed changes in it which he interprets as phases of a complicated life-cycle of *Spirochaeta pallida*. He considers the first stage of this cycle to consist of an aviscous form, which later develops into a homogeneous substance. When stained red by Giemsa's method, it becomes transformed into coccoid forms, and these eventually become transformed into accumulations of spirochetes.

PAUL R. CANNON

THE BACTERIAL FLORA OF THE SMALL INTESTINE IN PERNICIOUS ANEMIA IDA
LICHT, Zentralbl f Bakteriöl **115** 320, 1930

The duodenal contents of eight patients with pernicious anemia, obtained through the duodenal tube, gave constantly positive cultures of *Bacillus coli*, whereas in normal persons the cultures were sterile. The observations were positive both in the stage of relapse and in the remission after liver therapy. The observations in patients with acidity, catarrhal icterus, cholecystitis and cholelithiasis are also given.

PAUL R. CANNON

ON DISSOCIATION OF *B. TYPHOSUS* BY CULTIVATION IN TYPHOID-IMMUNE
SERUM G M FRAENKEL and M W STABNIKOWA, Ztschr f Immunitäts-
forsch u exper Therap **67** 539, 1930

In studying two strains of *B. typhosus*, the authors found that under the influence of typhoid-immune serum, a succession of constant variants appear that differ in antigenic, biologic and cultural characteristics from the other strain.

Although these variants have as a basis many common characteristics, they show individual peculiarities in relation to the receptor apparatus and their ability to split carbohydrates. One can see the common characteristics between these variants and the paratyphoid group (agglutination by paratyphoid serums, the zone of acid agglutination and the splitting of dextrose by gas formation), but as a whole the corresponding characteristics of the variants are not absolutely those of *B. paratyphosus* and, in general, cannot be placed in any distinct species of the colon-typhoid group.

AUTHORS' SUMMARY

Immunology

REACTIONS OF RABBITS TO NON-HEMOLYTIC STREPTOCOCCI C L DERICK,
C H HITCHCOCK and HOMER F SWIFT, J Exper Med **52** 1, 1930

The most satisfactory method thus far found for the induction and maintenance of a high degree of hypersensitiveness—"allergy," "hyperergy"—against non-hemolytic streptococci consists in the repeated production of small focal lesions with minimal doses of bacteria. After a preliminary sensitizing period of about two weeks' duration with either large initial, or small multiple daily inoculations, the later foci need be produced only at from seven to ten day intervals. Chronicity of low grade infection appears to be an important factor in the attainment of a high degree of hypersensitiveness.

AUTHORS' SUMMARY

ENHANCED PASSIVE IMMUNITY TO STREPTOCOCCUS INFECTION IN RABBITS
F P GAY and A R CLARK, J Exper Med **52** 95, 1930

The experimental work herein reported tends to justify our hypothesis recently expressed, that the common failure of antibacterial serums to combat active infections when passively transferred to a normal animal is due not so much to a lack of suitable or sufficient antibodies as to absence of cell preparation or

mobilization in the recipient. In the case of experimental streptococcus empyema in the rabbit the course of the ordinarily fatal infection is in no wise affected by the transfer of the pleural fluid containing large numbers of mononuclear cells derived from an animal that is itself protected as a result of a nonspecific irritation. The serum of a rabbit highly immunized against the streptococcus and containing antibodies for it produces relatively slight effect in prevention or cure. In contrast to this the pleural exudate, either acute (polymorphonuclear) or subacute (mononuclear), produced in an actively immunized animal does protect passively to a considerable degree. In a similar fashion normal exudate cells of either type in combination with the relatively ineffective antiserum give a high degree of protection. It remains for further analysis to determine whether this form of passive immunity by antiserum enhanced by the addition of cells depends on the vital properties of the cells transferred or on their stimulation to cell mobilization in the recipient. And furthermore the extent to which this enhanced passive immunity may be effective in cure, and whether the cure is applicable to local or to both local and generalized infection remain to be seen.

AUTHORS' SUMMARY

DEVELOPMENT OF AGGLUTININS AND PROTECTIVE ANTIBODIES IN RABBITS, AFTER INHALATION OF TYPE II PNEUMOCOCCI. ERNEST G. STILLMAN, J. Exper. Med. **52** 225, 1930.

Following repeated inhalations of the degenerated nonvirulent "R" forms of type II pneumococcus, no type-specific antibodies can be demonstrated in the serum of rabbits. Following repeated inhalations of slightly virulent type II (SA₁) pneumococci, only protective antibodies can be demonstrated in the serum of rabbits. Following repeated inhalations of virulent type II (S₁) pneumococci, agglutinins and protective antibodies can be demonstrated in the serum of rabbits. Following repeated exposures of rabbits to inhalation of pneumococci, the type-specific response, evidenced by type-specific protective antibodies and agglutinins, varies in direct proportion to the virulence of the culture used.

AUTHORS' SUMMARY

A TYPE SPECIFIC SUBSTANCE DISTINCT FROM THE SPECIFIC CARBOHYDRATE IN PNEUMOCOCCUS TYPE I. JOHN F. ENDLERS, J. Exper. Med. **52** 235, 1930.

Evidence has been presented for the existence of a substance distinct from the specific carbohydrate in the autolytic products of pneumococcus type I. The substance reacts specifically by precipitating homologous antiserum which either occurs naturally without antibody against the specific carbohydrate or has been deprived of that antibody artificially. In guinea-pigs passively sensitized with such antisera the homologous autolysate containing the substance alone produces typical lethal anaphylactic shock. In weakly alkaline solution the substance is destroyed by boiling. In weakly acid solution it resists a temperature of 100 C. for at least one-half hour. Autoclaving for one hour at 15 pounds' pressure in either acid or alkaline solution destroys its activity as precipitinogen. The substance is resistant to peptic digestion. The chemical nature and the possible identification of the substance as a hapten have been discussed.

AUTHOR'S SUMMARY

RESISTANCE OF NORMAL HUMAN BEINGS TO RECENTLY ISOLATED PATHOGENIC PNEUMOCOCCI. O. H. ROBERTSON and M. AGNES CORNWELL, J. Exper. Med. **52** 267, 1930.

With a view to obtaining information as to the virulence of pneumococci for human beings, a study was made of the pneumococidal action of normal human serum-leukocyte mixtures for freshly isolated strains of pathogenic pneumococci. It was found that human beings as a group showed well marked pneumococcus-

destroying power in their blood for all types of organisms studied. Individuals, however, exhibited wide variations in their reactions against the different types. These ranged from marked killing effect for one type of pneumococcus to none or slight against another. While reactions against different strains within the type often varied considerably, this difference was less, on the whole, than that between types. An interpretation of these observations in the light of previous animal experiments in which actual determination of resistance to pneumococcus infection was made leads to the inference that human beings in general possess a considerable degree of natural immunity to all types of pneumococci but that individuals may be relatively susceptible to one or more types and at the same time resistant to others, also that pathogenic strains of pneumococci vary much in their virulence for man.

AUTHORS' SUMMARY

OPSONIC AND BACTERIOTROPIN ACTION. MAX STRUMIA, STUART MUDD, E. B. H. MUDD, B. LUCKE and M. McCUTCHEON, *J. Exper. Med.* **52** 299 and 313, 1930.

Antiserums against several strains of acid-fast bacteria have been separated into their euglobulin, pseudoglobulin and albumin fractions. The globulin fractions have been found to possess the essential properties of bacteriotropic serums, thus they alter the bacterial surface properties, and, in quantitative correspondence, cause agglutination and phagocytosis; these several effects withstand washing of the sensitized bacteria, the effects are little if at all affected by inactivation of the antiserums before fractionation, the combination of antibody and antigen is serologically specific. The conclusion is drawn that the contact of antigen with fresh homologous immune serum results in the deposit on the antigen surface of a substance or substances contained in the globulin fractions of the antiserum, as a consequence of this surface deposit leukocytes can spread on and engulf the antigen.

As a further test of the theory of tropin action proposed in the preceding paper, artificial surfaces have been prepared and have been found to be phagocytized according to prediction from the theory. Protein was adsorbed on collodion particles according to the technic of F. S. Jones. These particles were then agglutinated and prepared for phagocytosis by the corresponding protein precipitin serums. The precipitating, agglutinating, surface and tropin effects for each serum or serum globulin fraction have been found to be in satisfactory quantitative correspondence. All of these effects were serologically specific, all remained almost unaffected by inactivation of the immune serums for thirty minutes at 56 C or by washing of the particles after sensitization. The surfaces of particles maximally sensitized by homologous rabbit immune serum or one of its globulin fractions have shown certain characteristic properties, i. e., they were cohesive, had wetting properties characteristic for protein and were isoelectric at p_H 5.5 to 5.8. The same set of properties was found for immune precipitate in the zone of maximal precipitation. The same properties have also been found for maximally sensitized acid-fast bacteria, and for maximally sensitized sheep erythrocytes. These results indicate, we believe, that precipitation, agglutination, the surface changes and increased phagocytosis are all consequences of one underlying phenomenon. This phenomenon is the specific chemical combination with, and deposit on the surface of the antigen of antibody protein. The several serologic reactions then follow as consequences of the properties of the sensitized surface and of the special environing conditions. The antibody is contained in the globulin fractions of immune serum, and appears to be a globulin with physicochemical differences from normal serum globulin.

AUTHORS' SUMMARIES

EXPERIMENTS ON ANAPHYLAXIS TO AZOPROTEINS. K. LANDSTEINER and PHILIP LEVINE, *J. Exper. Med.* **52** 347, 1930.

Experiments with azoproteins containing stereochemical isomeric groups of d-tartaric acid and l-tartaric acid showed well marked specificity of the anaphy-

lactic reaction to these antigens, in conformity with the results of precipitin tests. Shock in these animals could be prevented by injection of azodye containing the specific groups. This phenomenon is ascribed to a desensitization.

AUTHORS' SUMMARY

THE RELATION OF NATURAL HUMORAL ANTIPNEUMOCOCCAL IMMUNITY TO THE INCEPTION OF LOBAR PNEUMONIA. O. H. ROBERTSON, EDWARD E. TERRELL, JAMES B. GRAESER and M. AGNES CORNWELL, J. Exper. Med. **52** 421, 1930.

A study of the pneumococciidal-promoting action of the serum of patients with lobar pneumonia, secured from four to forty-eight hours after the onset of the disease, has revealed the fact that in the majority of instances the serum possessed the power to promote killing of the homologous pneumococcus, isolated in different instances from the lung, blood and sputum. While in some instances this action was slight, in others it was present to as great a degree as in normal persons and persisted as long as forty-eight hours or more after the beginning of the disease. The variations observed from case to case were not related to the extent of the pneumonic lesion or to the virulence of the several pneumococcus strains but appeared to depend on differences in individual human beings in respect to the natural antipneumococcus properties of their blood and their reaction to the invading micro-organism. A constant relationship was found to exist between the concentration of immune properties in the serum and blood invasion. In the presence of a well marked pneumococciidal-promoting power pneumococci were not found in the blood stream, and only when this property was greatly diminished or lost did blood invasion occur. The observations, which are supported by certain previous experimental observations, indicate that lobar pneumonia can occur in the presence of a normal circulating antipneumococcus defense mechanism. From this it is inferred that before pneumococcus growth can be initiated there must be present in the lung local changes of such nature as to provide conditions for the multiplication of pneumococci protected from the pneumococciidal action of the blood. Suppositions as to the nature of these changes and the establishment of the pneumonic lesion are discussed.

AUTHORS' SUMMARY

IMMUNITY TO POLIOMYELITIS IN MOTHERS AND THE NEWBORN AS SHOWN BY THE NEUTRALIZATION TEST. W. LLOYD ALCOCK and S. D. KRAMER, J. Exper. Med. **52** 457, 1930.

Neutralization tests for the virus of poliomyelitis on blood serum of urban mothers and their new-born infants showed that immunity was present in ten of twelve (83 per cent) infants and in ten of twelve (83 per cent) mothers, with a complete correspondence between mother and infant. These tests point to passive transmission of immunity from mother to infant. Previous tests on other children (from 1 to 5 years of age) indicate that immunity in infants is transitory. Previous observations concerning the extent of immunity in urban adults are confirmed and extended. The results of these tests are in accord with the age distribution of poliomyelitis and parallel corresponding observations in diphtheria.

AUTHORS' SUMMARY

SPECIFIC PRECIPITATION AND MOUSE PROTECTION IN TYPE I ANTIPNEUMOCOCCUS SERA. MICHAEL HEIDELBERGER, RICHARD H. P. SHAW and FORREST E. KENDALL, J. Exper. Med. **52** 477, 1930.

A rapid and simple method is given for the approximate determination of the specifically precipitable protein in type I antipneumococcus sera. It is shown that a close parallel exists between the specifically precipitable protein and the number of mouse protection units in a wide variety of type I antipneumococcus sera. Owing to the consistent results obtained and the rapidity, simplicity and

economy of the method, its use is proposed instead of the mouse protection test as a basis for the titration of standard serums and the comparison of others with a standard. A method is given for conveniently preparing highly purified specific polysaccharide of type I pneumococcus.

AUTHORS' SUMMARY

THE EFFECT OF INFLAMMATORY REACTIONS ON TISSUE IMMUNITY. FRANKLIN M. HANGER, J. Exper. Med. **52** 485, 1930

Animals showing natural bacterial allergy to filtrates of *B. leptosepticum* survive infection by this organism more frequently than weak reactors. This increased resistance is manifested by better localization of infection. Bacterial filtrates injected into skin twenty-four hours before infection exert a nonspecific protection of that area against the organism, even in susceptible animals. The cells of this protected area seldom undergo necrosis when infected. Severe injury of tissues either by chemicals or by an antigen-antibody reaction produces a loss of local resistance even in immune animals. Mild injuries have the opposite effect. It is believed that in cases of severe injury, the affected areas undergo a segregation from the circulating antibodies. When bacterial-immune serum is injected with a protein antigen into the skin of a sensitized animal, a local alteration occurs in which substances necessary for the effective action of the immune serum are destroyed. A protective action is restored to the altered immune serum by addition of complement to the lesion. It is felt that allergy is not the chief mechanism in cellular resistance to infection, however, data are advanced which suggest that allergy does not exert local protection by acceleration of the immune processes and by rendering the cells locally refractory to further injury. Chronic infection by a single strain of organism excites cellular reactivity to many strains of bacteria often unrelated biologically. Hence a nonspecific mechanism for localizing infections throughout the body may be induced.

AUTHOR'S SUMMARY

SEROLOGICAL REACTIONS IN PNEUMONIA WITH A NON-PROTEIN SOMATIC FRACTION OF PNEUMOCOCCUS. WILLIAM S. TILLET and THOMAS FRANCIS, JR., J. Exper. Med. **52** 561, 1930

Serums from persons acutely ill with lobar pneumonia possess the capacity to precipitate in high titer a nonprotein somatic fraction derived from pneumococci (fraction C). Following crisis the reaction is no longer demonstrable. Serums obtained from cases of pneumococcus pneumonia during illness and convalescence have been tested for antibodies specifically reactive with three chemically distinct constituents of pneumococcus. The results, when correlated with the course of disease, demonstrate differences in the occurrence of each qualitatively distinct antibody. The precipitation of pneumococcus fraction C is not limited to the serums of persons ill with pneumococcus infection. But in the few other cases available for comparative tests, definite reactions have been obtained only in streptococcus and staphylococcus infections and in acute rheumatic fever.

AUTHORS' SUMMARY

CUTANEOUS REACTIONS IN PNEUMONIA. THOMAS FRANCIS, JR., and WILLIAM S. TILLET, J. Exper. Med. **52** 573, 1930

The majority of patients convalescent from pneumonia due to types I, II and III pneumococcus develop at the time of recovery circulating antibodies for the homologous type of organisms. At the same time an immediate wheal and erythema reaction followed the intradermal injection of the homologous type-specific polysaccharide in 100 per cent of type I patients, 58.8 per cent of type II patients and 44 per cent of type III patients. In a group of eighteen patients repeatedly tested with the type-specific polysaccharides, ten developed in the second or third week of convalescence circulating antibodies for one or more heterologous types.

In none of twenty-one control patients was this phenomenon observed. It is suggested that the development of circulating antibodies for heterologous types of pneumococcus was associated with the previous intradermal injections of the type-specific polysaccharides.

AUTHORS' SUMMARY

IMMUNOLOGICAL STUDIES IN RELATION TO THE SUPRARENAL GLAND J
MARMORSTON-GOTTESMAN, DAVID FLAIA and JEFFERSON VORZIMER,
J Exper Med 52 587, 1930

Bilateral suprarenalectomy in rats lowers the resistance to a subsequent infection with *T. lewisi*. Almost 70 per cent of these rats die within an average period of 58 days after infection. The multiplication of the parasites in the circulating stream is not more considerable than in rats previously normal, nor is the duration of the disease in the surviving rats any longer than in the normal group. Bilateral suprarenalectomy does not prevent the formation of immune substances to the parasites but appears to lower the natural resistance of the rat to the toxic effects of the protozoan infection. The acquired immunity to *T. lewisi* of normal rats as a result of infection is not broken down by subsequent suprarenalectomy. Unilateral nephrectomy does not affect the course of a subsequent infection with *T. lewisi*.

AUTHORS' SUMMARY

THE COMPLEMENT FIXATION TEST IN RELATION TO THE GONOCOCCUS AND
ALLIED ORGANISMS JOHN O. OLIVER, I Mag 29 259, 1929

Under experimental conditions, in rabbits, a considerable degree of cross-fixation between *Micrococcus catarrhalis* antiserums and gonococcal extracts occurs in complement-fixation tests. The degree of cross-fixation under these experimental conditions is also well marked with aberrant forms of *M. catarrhalis* bearing a close resemblance to the more typical organisms, but is slight with those organisms showing considerable variation from the typical strains. Similar experiments carried out with patients are less successful in producing such cross-fixation, probably owing to the limitation of dosage and the method of administration imposed. Naturally occurring infections with *M. catarrhalis* and aberrant forms of the organism introduce a danger of cross-fixation in gonococcal complement-fixation tests. Such results appear, however, to be the exception rather than the rule in such infections. Serums giving strongly positive reactions to the Wassermann test do not tend to react to the gonococcal complement-fixation test in the absence of a history or of signs of the disease, and no danger of falsely positive reactions arises as a result of preparing gonococcal extracts from patients suffering from syphilis in the secondary stage in addition to gonorrhea.

AUTHOR'S SUMMARY

THE TOXICITY OF HUMAN SERUM FOR THE GUINEA-PIG SUSAN G. RAMSDEIL
and I. DAVIDSON, J Immunol 18 473, 1930

When normal horse serum was used in large amounts as an antigen in the human being, the phenomenon of a toxicity of the serum of such treated persons for the guinea-pig was found to occur more regularly and to continue for a longer period of time than had been shown to be the case in our former experiments with serums of persons treated with various immune serums. This increase is attributed to the relatively large amounts of serum with which the patients were treated. Certain cases were found in which the serum taken at a pretreatment bleeding contained the factor for toxicity. This was usually, but not always, accompanied with a higher than normal (heterophil) agglutinin titer for sheep red cells. Such serums tended to become more toxic subsequent to treatment of the patient along with an increase of the agglutinin and hemolysin titers. When the serums of a group of seriously ill patients were tested, the phenomenon of toxicity

was found with considerable frequency, especially in those suffering from syphilis and acute infectious processes. In 50 per cent of the serums of the last, the toxicity was correlated with the presence in the serum of heterophil antibody (sheep cell agglutinin in a titer above that normally found). It is evident that the toxicity of human serum for the guinea-pig must be ascribed to two or more different factors in the serum—one of these its content in heterophil antibody, the other as yet undetermined.

AUTHORS' SUMMARY

QUANTITATIVE RELATIONS IN AGGLUTINATION AND PRECIPITATION HANS ZINSSER, *J Immunol* **18** 483, 1930

Zinsser would explain why agglutinating serum can be active in very much higher dilution than precipitating serum by assuming that in each case the anti-serum must coat with its globulin the surfaces of the antigenic particles. Now the total surface of antigenic particles concerned in the precipitation test is estimated to be at least 10,000 times greater than the surface of the bacteria concerned in agglutination, and consequently a given serum might be diluted 10,000 times higher without losing its agglutinating power than could be done before it loses its power of precipitating colloidal antigenic particles. This explanation would eliminate objections to the unitarian conception of antibodies based on the fact that agglutinating serum can be diluted many more times without losing its agglutinating effect while its precipitating effect ceases on comparatively slight dilution.

BLOOD GROUP DISTRIBUTION AMONG POLYNESIANS CLARA NIGG, *J Immunol* **19** 93, 1930

The incidence of the four blood groups among 413 full-blooded Hawaiians was found to be as follows: group O, 36.5 per cent, group A, 60.8 per cent, group B, 2.2 per cent, group AB, 0.5 per cent. The A agglutinin was found in 100 per cent of the 237 group A Hawaiian bloods examined for this factor. This incidence is in contrast to 80 per cent found in the white race.

AUTHOR'S SUMMARY

USE OF BROTH CULTURE FILTRATES IN ANAPHYLAXIS EXPERIMENTS JOHN Y. SUGG and JAMES M. NEILL, *J Immunol* **19** 145, 1930

Experiments were made on two questions. First, the primarily toxic (anaphylactoid) action was studied by intravenous injection of normal guinea-pigs with formaldehyzed and unformaldehyzed filtrates of diphtheria and other bacilli and with the nonbacterial constituents of the filtrates (uninoculated broth, solutions of phenol and of formaldehyde). The possibility of sensitization to the nonbacterial constituents during immunization with the filtrates was studied by intravenous tests on animals previously given repeated subcutaneous injections of formaldehyde solution or of formaldehyzed broth. With diphtheria filtrates, neither the primary toxicity nor the possibility of sensitization to the broth constituents, introduced significant complications in their use as material for active sensitization and for subsequent intravenous tests. The adaptability of broth culture filtrates of other bacteria to anaphylaxis experiments would depend on the quantitative effectiveness of the antigens they liberate into their culture fluids.

AUTHORS' SUMMARY

RENAISSANCE OF PRE-EHRlich IMMUNOLOGY W. H. MANWARING, *J Immunol* **19** 155, 1930

There is convincing evidence that injected antigens undergo a series of chemical "hybridizations" in animal tissues, and suggestive evidence that the resulting antigen-tissue "hybrids" become semipermanently "symbiotic" with these tissues, both terms, of course, being used metaphorically. Whether or not these "symbiotic hybrids" are to be regarded as partially homologized antigens, as specifically

alienated somatic proteins or as antigen-somatic-protein conjugates cannot be predicted from present biochemical knowledge. There is convincing evidence that some of these antigen-tissue "hybrids" have properties simulating those of specific antibodies, but no proof thus far that they are identical with these antibodies. There is, however, no evidence at the present time that there is any other physiologic method of specific antibody formation.

AUTHOR'S SUMMARY

ON THE NATURE OF THE THERMOSTABLE PRECIPITINS. DINO D. NAI, *J. Immunol.* **19**, 255, 1930.

The agglutinin of Joos, the thermostable precipitinogen of Aseoli, the residue antigens of Zinsser and the carbohydrate material of the American observers may be representatives of a single class of antigens. Their serologic reactions are parallel and their common characteristic is heat stability. On these grounds it is possible that the carbohydrate nature of the soluble specific substance of the American observers may also exist in the antigens of Aseoli, Joos and Zinsser. Indeed, this idea is supported by the recent experiments of Schockaert. He found that the thermostable antigen involved in the Aseoli reaction with anthrax bacilli, whether pure cultures of the micro-organism or organs of anthrax-infected animals are employed, is a polysaccharide similar to that of the soluble specific substance of pneumococci, or of other bacteria.

AUTHOR'S SUMMARY

ANTIGENS FROM CULTURES OF *TRYPANOMA PALLIDUM*. AUGUSTUS B. WADSWORTH, J. LANE E. VAN AMSTER and MARGARET W. BRIGHAM, *J. Immunol.* **19**, 289, 1930.

One strain of *Spirochaeta pallidum* was used for this study. By the aqueous extraction of the organisms, antigenic substances were obtained which reacted with serums of rabbits immunized with the homologous strain, but not with syphilitic rabbit or human serums. Cholesterol added to various extracts of the organisms did not increase their sensitivity, and alcoholic extracts were anti-complementary. The antigenic substances obtained by aqueous extraction of the organisms appear to differ from those obtained by alcoholic extraction. Substances that reacted with rabbit immune serum and rabbit and human syphilitic serums were found in alcoholic extracts of the culture medium, and similar extracts of mediums containing the spirochete were more active. Cultures of spirochetes produced complement-fixing substances like those obtained by aqueous extracts of spirochetes free from medium.

E. DELVES

COMPLEMENT AND OPSONIN. J. GORDON, *J. Immunol.* **19**, 303, 1930.

Congo red and similar dyes prevent the bactericidal and hemolytic (complement) activities of normal serum. A serum the complement of which has been inactivated by certain concentrations of congo red is still able to exert its opsonic activity.

AUTHOR'S SUMMARY

ON THE PRODUCTION OF TYPHOID AGGLUTININS. C. A. BIERRENS and C. H. KEIPER, *J. Immunol.* **19**, 321, 1930.

Frequency of injections plays a major role in typhoid agglutinin production. A close relationship exists between the interval of injections and the dose employed. Total amounts of agglutinin injected have but little direct influence, however, some indirect influences are apparent. The axiom of frequent stimulation of the body cells of the animal by the use of small doses of agglutinin and by larger doses as the intervals between inoculations are increased is emphasized. Typhoid agglutinins with greatest potencies are produced by injecting 0.1 cc frequently, 1 cc less frequently and 5 cc still less often. Typhoid agglutinins with high titers are possible with any of the three doses studied, the highest, however, follow the

employment of the largest dose Typhoid agglutinins of equal potencies are elaborated irrespective of dosage, when inoculations are made every third day Increasing the dose with each subsequent injection results in agglutinins with much higher titers than when the reverse is true Nonspecific agglutinin formation is negligible Physical deterioration of the rabbits shows its effect on agglutinin production Comparable results are obtained with various agglutinogens, precipitinogens and lysinogens

AUTHORS' SUMMARY

IS IMMUNITY TO SCARLET FEVER A FACTOR IN PUERPERAL SEPSIS? LELAND W PARR, *J Prev Med* 4 105, 1930

A very favorable puerperal morbidity rate (9.33 per cent) was observed in a study of more than 1,000 deliveries in the hospital of the American University of Beirut, Syria, a region of high scarlet fever immunity The question is raised as to the possibility of this favorable rate being due to a group immunity within the streptococcus group

AUTHOR'S SUMMARY

THE RESISTANCE TO POLIOMYELITIS OF ANIMALS PREVIOUSLY INOCULATED WITH HEATED VIRUS HOWARD J SHAUGHNESSY, PAUL H HARMON and FRANCIS B GORDON, *J Prev Med* 4 157, 1930

Monkeys that had received single intracerebral inoculations of poliomyelitis virus heated at from 42.5 to 55 C for from five to sixty minutes failed in most instances to show an appreciable degree of immunity to subsequent inoculation with active virus There are, however, indications that those monkeys that had received the virus heated at 45 or 50 C were relatively immune Attempts to immunize monkeys with repeated inoculations of virus did not prevent paralysis, but on the contrary seemed to heighten predisposition Apparently, however, the case-fatality rate was lowered

AUTHORS' SUMMARY

IMMUNITY TO INFANTILE PARALYSIS W LLOYD AYCOCK and S D KRAMER, *J Prev Med* 4 189, 201, 1930

Additional observations are recorded concerning immunity to poliomyelitis as indicated by the neutralization of the virus by the blood serum of persons who had had an attack of the disease, monkeys that had passed through the experimental disease, monkeys immunized with the virus, normal monkeys and normal persons of different ages from urban and rural populations These tests in normal individuals are in conformity with extended previous observations that a widespread immunity to poliomyelitis exists among individuals not known to have had the disease Additional evidence is afforded that this immunity originates in exposure to the virus and, from the extent to which it occurs and the order in which it develops, that the virus spreads by contact of person with person

Serums of twenty-one adults from Atlanta, Georgia, having no history of poliomyelitis, unquestionably neutralized poliomyelitis virus in eighteen instances, and failed to neutralize it in two instances, the results with the other serum were not clearcut, but apparently this serum should be counted as having neutralizing power These tests indicate that immunity to poliomyelitis is equally extensive in warmer and cooler climates, and therefore suggest that the extent of the distribution of the virus in warmer climates is equal to that in cooler climates

AUTHORS' SUMMARY

THE RELATIVE INSUSCEPTIBILITY OF YOUNG RABBITS TO STREPTOCOCCAL TOXIN H J PARISH and C C OKELL, *J Path & Bact* 33 527, 1930

When small rabbits (from 0.33 to 1 Kg) and large rabbits (2 Kg) are given intravenous injections with suitable doses of broth cultures of scarlet fever strepto-

cocci or scarlet fever toxin, the small rabbits survive for significantly longer periods. The relative insusceptibility of small rabbits to streptococcal toxin is paralleled to some extent by the observations of Cooke and others on the Dick test in young children. The susceptibility of small rabbits could not be increased by artificial sensitization.

AUTHORS' SUMMARY

PHAGOCYTOSIS BY BRONCHIAL EPITHELIUM IN THE LUNGS OF MICE E S DUTHIE, *J Path & Bact* **33** 547, 1930

Phagocytosis of red blood cells in the bronchi of the lung has been described in a case of extreme passive congestion in a mouse following irradiation. The phagocytic cells have been identified by their morphologic and tinctorial appearance, as well as by the compensatory hyperplasia in the surrounding epithelium, as being of epithelial origin. Bronchial dust cells have been studied in healthy mice and a multiplication in their number followed on the inhalation of carbon particles. From the evidence it is considered that these are also of epithelial origin.

AUTHOR'S SUMMARY

EXPERIMENTAL STREPTOCOCCAL INFECTION AND IMMUNITY A W DOWNIE, *J Path & Bact* **33** 563, 1930

Lesions in rabbits injected with living cultures of Dick and Dochez strains of scarlatinal streptococci were similar to those produced by toxin of the Dochez strain except for the localization of organisms in joints and muscles, and anemia and hemolysis in animals injected with living culture. The course of infection following intravenous injection of streptococci is described, and the effect of age and the virulence of the injected culture noted. Intradermal injection of the moderately virulent Dochez strain in fatal cases caused only a slight local reaction, and invasion of the blood stream was rare. In a highly virulent erysipelas strain the lesions were more extensive, and the blood stream was invaded some time before death.

Rabbits immunized with Dochez strain toxin were protected against death from the injection of the culture of this strain. The Dick scarlatinal strain acted similarly, and there was no evidence of protection against heterologous strains. Immunization with heat-killed cultures yielded no protection. No antitoxin or protection for mice was found in the serums of animals immunized with toxin or heat-killed cultures. The immunization with a toxin of a virulent strain gives no protection for the homologous or heterologous strains, but gives some protection against less virulent strains.

Filtrates of strains of high and low virulence show no difference as judged by skin tests. Rabbits repeatedly injected with killed cocci of the virulent erysipelas strain gave protection against the homologous strain but not against the moderately virulent Dochez strain. The serums of these animals protected mice against homologous, but not heterologous, strains.

It would seem that with the highly toxigenic, moderately virulent scarlatinal strains used, the action is antitoxic rather than antibacterial, with highly virulent strains, however, effective immunity would appear to be antibacterial rather than antitoxic, and type specific.

FROM AUTHORS' SUMMARY

BACTERIOPHAGE ACTIVITY AND THE ANTIGENIC STRUCTURE OF BACTERIA F M BURNET, *J Path & Bact* **33** 647, 1930

Lysis by bacteriophage requires a preliminary adsorption of the phage particles to the bacterial surface. Evidence has been given to show that the adsorption is highly specific and that the nature of the bacterial surface in respect of this adsorptive power is the chief factor determining whether the organism will be lysed by a given phage. The bacterial surface constituents responsible for the specific

adsorption of phage are not destroyed by heating to 100 C and show a striking but incomplete parallelism in their functional aspects with the heat-stable agglutinogens. Organisms with similar heat-stable antigens despite wide differences in other respects show similar reactions toward bacteriophage and when the normal heat-stable antigen is replaced by another in the S-R transformation, a striking change in behavior toward phage occurs. On this evidence the hypothesis was put forward that bacteriophages and stabilotropic agglutinins were both specifically adsorbed to the same surface elements of bacteria. Further work showed that this hypothesis was inadequate to account for two groups of facts that some phage-resistant variants may show no serologic change and that serologically identical rough strains often show differences in phage reactions which can be related to the differing phage reactions of their smooth strains of origin. From a detailed study of the phage reactions and antigenic structure of various derivatives of three bacterial species, *B. sanguinarum* as a typical *Salmonella*, the Flexner type of dysentery bacilli and a white staphylococcus, an attempt is made to represent diagrammatically the constitution of the surface elements involved in the two types of function. The connection between the two functions is so intimate that one is justified in assuming that a single unit is responsible for both. In the *Salmonella* group this unit must be of considerable complexity to allow for the "unmasking" effect which is characteristic both of serologic and of phage reactions, when the S-R change takes place. The conditions in the particular staphylococcus studied seem to represent a simpler form of mosaic antigenic structure.

AUTHOR'S SUMMARY

OBSERVATIONS ON THE VARIANTS OF *B. SUBTILIS* AND THEIR RELATION TO THE SOMATIC AND FLAGELLAR ANTIGENS. N. C. GRAHAM, *J. Path. & Bact.* **33** 665, 1930

Four variants of *B. subtilis* (two motile and two, as a rule, nonmotile) have been obtained by selecting colonies on agar of different appearance. I and III form smooth, round, shiny colonies with regular margins, II forms "medusa-head" colonies and IV slightly irregular colonies with uneven surface and a somewhat granular texture. None of these variants has the distinctive characters of the R variants of *B. typhosus*, *paratyphosus*, etc. All four variants have the same heat-stable (100 C) somatic antigen for which corresponding somatic agglutinins can be obtained. Only one somatic antigen has been demonstrated in the four variants of the three strains which have been examined in detail. Variants I and II are motile and contain, in addition, a heat-labile (100 C) H or flagellar antigen and agglutinate with appropriate H agglutinins in a characteristic flocculent manner. The H antigen is the same for both motile variants. Variants with "medusa-head" colonies occur independently of any serologic or antigenic change. The nonmotile variants III and IV are coherent and viscous. They correspond when completely nonmotile to the O variant of Weil and Felix. The I and III variants consist of short bacilli. In IV the bacilli are perhaps somewhat longer than in I and III. Variant II, which forms "medusa-head" colonies, consists chiefly of very long rods, threads and chains. Of seven strains examined, only three agglutinated with the serums made from one of them, the remaining four did not appear to have any common antigen with those used to make serums.

AUTHOR'S SUMMARY

THE ACTION OF CERTAIN DYES ON THE BACTERICIDAL ACTIVITY OF NORMAL SERUM AND ON HAEMOLYTIC COMPLEMENT. J. GORDON, *J. Path. & Bact.* **33** 689, 1930

The action of congo red in interfering with complement activity is not due to its adsorption to the red cell. The inhibitory effect of congo red on complement can be removed by adding adsorbing agents, e. g., charcoal, heated serum, serum albumin or serum globulin. The congo red is adsorbed on the complement and most probably on the serum protein.

AUTHOR'S SUMMARY

TRANSMISSION OF MATERNAL IMMUNITY J H MASON, T DALLING and W S GORDON, *J Path & Bact* **33** 783, 1930

In sheep, beef, dog and horse no evidence of placental transmission of antitoxin was obtained

THE VIRULENCE TYPES OF STREPTOCOCCI AND THEIR IMMUNOLOGIC RELATIONSHIPS H DOLD and H R MUIR, *Zentralbl f Bakteriol* **114** 275, 1929

The authors retested by intracutaneous injections into rabbits the virulence of strains of streptococci which had previously been classified in three grades of virulence on the basis of similar tests several months before. They noted a marked tendency for the organisms to maintain their type virulence. Furthermore, immunization against a lethal dose of the most virulent type was possible not only with the same strain but also with strains from the two less virulent types, thus indicating the lack of any marked difference in antigenic properties of strains of various degrees of virulence.

PAUL R CANNON

RELATIONSHIP BETWEEN HERPES AND VACCINIA IMMUNITY E GILDEMEISTER and PAUL HIGERS, *Zentralbl f Bakteriol* **114** 314, 1929

Further experiments tend to confirm the earlier ones of Gildemeister and Herzberg concerning the immunologic relationships between herpes and vaccinia. In a considerable percentage of experimental animals, vaccinia immunity exerts a protective effect against a herpes infection and herpes immunity exerts a similar effect against vaccinia infection. This protective effect is not especially high, but nevertheless is definitely present.

PAUL R CANNON

T-ERYTHROCYTES AND T-AGGLUTININS C HALLAUER, *Ztschr f Immunitätsforsch u exper Therap* **67** 15, 1930

In 1927, Thomsen showed that under certain circumstances human red cells undergo such changes that they are agglutinated by human serum of all groups. Subsequently it was found that this change may be caused in various red cells by certain bacteria and their culture filtrates. The red cells are said to acquire a new receptor, "T," corresponding to which "t-agglutinins" exist in human and certain other normal serums. Hallauer has succeeded in immunizing rabbits and guinea-pigs with T-erythrocytes. The newly produced T-agglutinins are specific so far as they are absorbed only by T-erythrocytes.

A COMMON ANTIGEN IN HUMAN RED CELLS AND IN SHIGA'S BACILLUS M EISLER, *Ztschr f Immunitätsforsch u exper Therap* **67** 38, 1930

The serum of a goat immunized with Shiga bacilli agglutinated human red cells of all groups and various strains of Shiga bacilli absorbed from immune goat serum the agglutinin for the bacilli as well as the agglutinin for red cells. The red cells, however, removed only the hemagglutinin.

THE INFLUENCE OF ANTIRABIC INOCULATIONS ON EXPERIMENTAL TUBERCULOSIS IN GUINEA-PIGS M P GLUSMAN and J I GOLDENBERG, *Ztschr f Immunitätsforsch u exper Therap* **67** 187, 1930

Antirabic inoculations do not accelerate the course of tuberculosis, and immunity to rabies develops as usual in tuberculous guinea-pigs.

THE ANTIGENIC PROPERTIES OF BACTERIOPHAGE T YOSHIZUMI, K NAGASE and S HOSOYA, *Japanese J Exper Med* **8** 215, 1930

Using a new method of purification, the bacteriophage yielded none of the color reactions for proteins and it contained only an extremely small amount of

nitrogen The purified phage had as high a lytic power as the nonpurified No difference could be found in the antigenic qualities of the purified and the unpurified phage The purified phage does not act as a anaphylactogen or precipitinogen in its immune serum The hypothesis that phage is a chemical, nonprotein substance is upheld

Tumors

PRIMARY SYMPATHICOBLASTOMA OF THE SKIN OF THE THIGH VICTOR C JACOBSEN and KIYOSHI HOSOI, *Am J Path* 6 427, 1930

A case of sympathicoblastoma, primary in the skin or subcutaneum of the thigh of an infant, aged 9 months, is here reported There was a recurrence in the same location within six months So far as we have been able to determine, this is the only instance of a sympathicoblastoma occurring in such an unusual location At the present writing, almost two years after the removal of the recurrent tumor, the child is vigorous, robust and apparently normal in every respect

AUTHORS' SUMMARY

THE SIGNIFICANCE OF THE MUSCULAR "STROMA" OF ARGENTAFFIN TUMORS (CARCINOIDS) P MASSON, *Am J Path* 6 499, 1930

Originating in the nerves of the mucosa, previously hypertrophied, carcinoids penetrate the myenteric plexuses progressively without destroying them and without provoking their hyperplasia They merit the name of neurocarcinoid Invasion of the connective tissue and of the lymphatics is secondary Connective tissue infiltrated by carcinoids does not originate muscle fibers On the contrary, when the nerves are invaded by carcinoids, the corresponding muscle coats undergo hyperplasia restricted to the territory of the infected nerve The muscle fibers formed in the interstices of carcinoids, then, are not an integral part of these tumors, they result from proliferation of preexisting muscles provoked by the presence of argentaffin cells in their nerves This myogenic action of the argentaffin cells seems due to a product of limited diffusibility secreted by the cells into the nerves (neurocrinia) As a working hypothesis, one may suppose that the normal argentaffin cells of the intestinal mucosa function like the cells of carcinoids, and that their secretion poured into the plexus of the mucosa plays a rôle in the functioning of the muscularis mucosae

AUTHOR'S SUMMARY

DIAGNOSIS OF INTRACRANIAL TUMORS BY SUPRAVITAL TECHNIQUE LOUISE EISENHARDT and HARVEY CUSHING, *Am J Path* 6 541, 1930

The supravital technic has been adopted as the most favored routine method of diagnosing and classifying tumors of the central nervous system, it being of particular value in the cytologic differentiation of the various types of gliomas Not only can an immediate diagnosis be given to the surgeon so that he may learn to associate the microscopic type of the lesion with its gross appearance at the operating table, but a permanent photographic record of the fresh preparations can be made for comparison with the permanent section of the fixed tissue The supravital method makes it possible for the examiner to see the cells with their cytoplasm and processes intact and gives pictures which are wholly unfamiliar to those who have only studied these cells in fixed sections

AUTHORS' SUMMARY

SKELLETAL METASTASES IN CARCINOMA OF THE THYROID ISAAC LLVIN, *Am J Path* 6 563, 1930

Three cases of metastases in the skeleton secondary to carcinoma of the thyroid are reported In all three cases the clinical symptom complex as well as the

evident pathology was caused by tumors in the bone. While the primary tumor in the thyroid was insignificant, pathologically as well as clinically, compared with the condition in the skeleton, as a result in all three cases, the primary condition was overlooked. Whenever a diagnosis of malignant tumor in the skeleton, single or multiple, is made, a search must be undertaken for a primary malignant tumor elsewhere before the diagnosis of a primary malignant tumor in the skeleton can be made. In such a search for a primary malignant tumor, in a female, next to the breast, the thyroid must be thought of, and in a male, next to the prostate, the thyroid must be considered as the most probable seat of a primary tumor. Such a diagnostic analysis is of importance not only from the theoretical but also from the practical clinical standpoint.

AUTHOR'S SUMMARY

BIOPSY BY NEEDLE PUNCTURE AND ASPIRATION. H. E. MARTIN and E. B. ELLIS, *Ann Surg* **92** 169, 1930

Aspiration of tumor masses through an 18 gage needle by a syringe avoids dissemination of tissue, hemorrhage, infection and scars in visible areas. This method has led to a correct diagnosis in 60 per cent of sixty-five cases examined. These included tissues obtained from the neck, intrum, lungs, breast and bones. The method of preparing the specimen for immediate and paraffin section is also given.

RICHARD A. LIVINGDAHL

MALIGNANT TUMORS AND THEIR METASTASES. I. E. McWHORTLER and A. W. CLOND, *Ann Surg* **92** 434, 1930

This article represents a summary of 865 autopsies at Bellevue Hospital of New York, on malignant tumors, which comprised 6 per cent of 13,500 necropsies, covering a period of twenty-three years. The location of the primary tumor and the occurrence of regional and distal metastases are tabulated and discussed.

RICHARD A. LIVINGDAHL

FAILURE OF SPLEEN FROM TUMOR-BEARING ANIMALS TO PRODUCE TUMORS. W. H. WOGLOM, *J. Cancer Research* **13** 305, 1929

Experiments were reported by some German observers, in which the injection of an emulsified spleen from tumor-bearing rats into normal rats was sometimes followed by the appearance of a tumor in the healthy rodents. The experiments, if confirmed, are of interest in that they would destroy the established conception that cancer can be transmitted only by virtue of its cellular elements.

In a series of experiments, which he describes in detail, Woglom could not corroborate the observations of the continental worker. He is wondering whether the splenic tissue from the tumor-bearing rats used in Germany did not contain metastases at the time of transplantation.

R. M. FIELD

SPONTANEOUS MAMMARY CANCER IN MICE. MILFORD C. MARSH, *J. Cancer Research* **13** 313, 1929

Marsh studied two lines or strains of albino mice which spontaneously develop cancer of the breast. One strain yields the tumor in about 90 per cent and the other in about 55 per cent of the breeding females. These strains showed by mere inspection convincing evidence of heredity in various characters, including the disease cancer. Crosses of these strains with wild mice showed for cancer inconclusive evidence of simple mendelian inheritance with dominance.

In general, Marsh is of the opinion that the origin of tumors in mice is controlled by heredity and is affected as well by many environmental factors, some of which are little known or commensurable. This tends to obscure the genetic

interpretation It is probable that the expression of the tumor in heterozygotes is variable, and mendelian dominance or recessiveness is not sharply defined

B M FRIED

THE ACTION OF CERTAIN DYESTUFFS ON THE GROWTH OF TRANSPLANTABLE TUMORS K SUGIURA and S R BENEDICT, J Cancer Research **13** 340, 1929

Following the early experiments of Wassermann and his associates to the effect that by injecting a solution of selenium-eosin into the blood stream of cancerous mice the eosin would carry colloidal selenium into the tumors, numerous workers attempted to treat cancer-bearing animals with dyes The results obtained were contradictory, or negative Sugiura and Benedict studied the influence of a preliminary treatment in vitro of certain dyestuffs on the subsequent growth of malignant neoplasms in rats and chickens For their elaborate experiments they found that malachite green possessed the greatest destructive action on the tumors studied and congo red the least, while methylene blue (methylthionine chloride, U S P) and gentian violet were intermediate in action The harmful action of the dyestuffs is at least partially due to the selective staining reactions, i e, the adsorption of dye by proteins of tumor elements, and to the effect of the hydrogen ion concentration of the dye solutions

B M FRIED

ON THE FAILURE IN HETEROPLASTIC TRANSPLANTATION OF HUMAN MAMMARY CARCINOMAS INTO THE BRAINS OF RATS JOHN J MORTON, J Cancer Research **13** 359, 1929

Morton attempted to transplant human mammary cancer into the brains of albino rats Two hundred rats and twenty different human breasts with actively growing cancer were used in the experiments In no instance did a tumor develop in the brains of the rodents The inoculated neoplastic tissue was found to be transformed into hyalinized connective tissue

B M FRIED

THE CARCINOGENIC ACTIVITY OF TAR IN VARIOUS DILUTIONS W H WOGLOM and L HERLY, J Cancer Research **13** 367, 1929

The authors attempted to induce cancer in mice by painting their backs with various dilutions of tar in glycerin They found that a dilution down to 25 per cent neither retards the appearance of malignant tumors nor diminishes the number induced However, the mortality of the experimental animal is about 50 per cent lower when the diluted tar is used

B M FRIED

SPONTANEOUS TUMORS OF THE RAT F D BULLOCK and M R CURTIS, J Cancer Research **14** 1, 1930

Within a period of ten years, in a colony of about 10,000 rats, the authors have found 2,450 rats each bearing 1 or more cysticercus tumors and 489 rats with tumors which arose independently of the direct stimulation of the parasite Sarcoma was by far the most common form of malignant new growth There were 63 carcinomas, 35 of which were of the squamous cell type, involving the skin in 24 rats, the uterus in 10 and the lung in 1 There also were mixed tumors and rare tumors, such as chondrorhabdomyosarcoma and ostochondrosarcoma

The superficial tumors rarely metastasized, but the more deeply seated tumors not infrequently formed metastases

Of 212 benign tumors, 87 originated in the mammary gland in contrast to the low incidence of cancer of the breast Seventy-four tumors arose in the thymus and of these 68 were benign

An interesting trait of the rat neoplasms was the comparatively frequent occurrence of a malignant transformation of the fibrous tissue elements in the benign

fibrous and fibro-epithelial tumors and also in the malignant epithelial tumors. The occurrence of primary multiple tumors was also not as rare as one finds in the literature. There were very few primary pulmonary tumors.

B M FRIED

URANIUM-THORIUM COLLOID IN THE TREATMENT OF CARCINOMA G T PACK and F W STEWART, *J Cancer Research* **14** 152, 1930

The authors treated eight patients with intravenous injections of uranium-thorium after the manner recommended by Hockins. There was no evidence of improvement following the treatment. In two patients the chemical was found deposited in the Kupffer cells and in the reticulo-endothelial cells of the spleen. In these cases the desiccated livers and spleens were radioactive, whereas the desiccated tumor tissues showed no evidence of radioactivity.

B M FRIED

THE AGE AND SEX DISTRIBUTION AND INCIDENCE OF NEOPLASTIC DISEASE AT THE MEMORIAL HOSPITAL, NEW YORK CITY G T PACK and R G LEFEBvre, *J Cancer Research* **14** 167, 1930

Of 19,129 tumors studied at the Memorial Hospital, New York, within a period of twelve years, 16,565 were malignant. Of these 89.6 per cent were epithelial and 10.4 per cent of connective tissue origin (sarcomas). The average age of patients with carcinoma was 53.9 years, and of those with sarcoma, 38.2 years. Tumors of the brain were uncommon in old people. Fifty per cent of the gliomas were in subjects younger than 25 years. The average age of persons with Ewing's tumor was 22 years. Multiple myeloma occurred in patients of about 42 years. Cancer of the alimentary tract was four times as frequent in men as in women. Cancers of early life, as in the breast, stomach, tongue and rectum, progress more rapidly, disseminate more frequently and recur more often after removal than do their congeners of adult life. Radiosensitivity is a property found frequently in the malignant neoplasms of youth.

This article, which occupies practically the entire number of the *Journal of Cancer Research*, abounds in tables and figures. It is only partially abstracted.

B M FRIED

THE BLOOD CHEMISTRY OF HENS BEARING ROUS SARCOMA No 1 J H ROE and ELLEN M DYER, *J Cancer Research* **14** 301, 1930

Twelve hens bearing Rous sarcoma no 1 showed no change in the nonprotein nitrogen, uric acid, creatinine, chlorides, cholesterol, serum calcium and inorganic phosphorus, hemoglobin and bilirubin of the blood. The analyses were performed at times varying from eighteen days before death to the day of death. The blood sugar of the sarcomatous hens was found to be elevated. There was a questionable lowering of the carbon dioxide combining power of the blood of the tumor-bearing birds.

B M FRIED

A CRITICAL STUDY OF VITAMIN A AND CARCINOGENESIS K SUGIURA and S R BENEDICT, *J Cancer Research* **14** 306, 1930

For about eighteen months the authors followed up 108 rats fed a diet deficient in vitamin A, to ascertain whether such alimentary regimen would play a role in the development of tumors in these rodents. The results obtained are to the effect that the prolonged maintenance on a deficient diet has no apparent influence on tumor genesis in these animals.

B M FRIED

THE INFLUENCE OF HIGH DIETS ON THE GROWTH OF CARCINOMA AND SARCOMA IN RATS K SUGIURA and S R BENEDICT, *J Cancer Research* **14** 311, 1930

The percentage of positive tumor inoculations and the growth rate of Flexner-Jobling rat carcinoma in rats were diminished, and the number of tumor regres-

sions were increased, by feeding the animals with an excessive amount of butter fat (over 26 Gm daily)

Ingestion of a high fat diet failed to show any inhibiting or accelerating influence on the growth of Sugiura rat sarcoma

The number of takes and the growth rate of rat carcinoma and rat sarcoma were not affected by feeding animals with a fat-free diet

The vitamins A, C, D and E are not essential for the growth of transplanted neoplasms

AUTHORS' SUMMARY

THE CATALYTIC EFFECT OF METHYLENE BLUE ON THE OXYGEN CONSUMPTION OF TUMORS AND NORMAL TISSUES E S GUZMAN BARRON, J Eaper
Med 52 447, 1930

Methylene blue (methylthionine chloride, U S P) has no catalytic effect on the oxygen consumption of the normal adult tissues that do not possess aerobic glycolysis The dye increases the oxygen consumption of these tissues when their respiration has been inhibited by the addition of potassium cyanide and their fermentative power has thus been brought into action Methylene blue increases the oxygen consumption of normal tissues having aerobic glycolysis, and of tumors The effect of methylene blue is roughly proportional to the fermentative power of tissues

AUTHOR'S SUMMARY

STUDIES OF DISEASES OF THE LYMPHOID AND MYELOID TISSUES HENRY JACKSON, JR, FREDERIC PARKER, JR, and EUGENE C GLOVER, J Eaper
Med 52 547, 1930

From a study of the metabolism of seventy-one lymph nodes and tumors one may conclude The nature of a tumor cannot be predicted from the metabolism because too much overlapping of metabolic rates exists between the pathologic groups There is no evidence metabolically one way or another as to whether malignant lymphomas of any type should be classed as neoplastic or as infectious processes The degree of cell differentiation can in most cases be foretold by the percentage difference between the aerobic and the anaerobic glycolysis The greater the differentiation the greater is the percentage difference Sarcomas in general constitute an exception to this rule The degree of malignancy in carcinoma, but not in other tumors, can, with certain exceptions, be predicted from the height of the value U Human sarcomas appear to have a metabolism far more closely comparable to that of benign tumors than to that of carcinomas They do not behave as malignant tumors under the Warburg classification Their energy requirements are not of the same order as those of carcinoma One cannot from the value U or from the glycolytic rates predict whether or not a tissue should be classed as neoplastic Warburg's observations on carcinomas are confirmed and amplified

AUTHORS' SUMMARY

CARCINOGENIC SUBSTANCES AND THEIR FLUORESCENT SPECTRA E L KENNAWAY and I HIEGER, Brit M J 1 1044, 1930

Heat was found to be a factor in producing carcinogenic substances in acetylene, isoprene, cholesterol, human skin, muscle and hair, and in yeast These substances caused cancer in mice While working with substances of a carcinogenic nature at body temperatures, the authors found these producing typical spectra in the 4,000 to 4,400 Angstrom unit bands At times there was some confusion in the bands because certain impure hydrocarbons apparently contained several fluorescent compounds Some fluorescent substances did not produce cancer, and several explanations are offered to account for the fact There may be this spectrum produced by carcinogenic and also noncarcinogenic substances Also the fluorescent test is very delicate, often appearing in dilutions of 1 200,000,000, in which strength

it could not reasonably be expected to produce cancers in mice. It is suggested that a spectroscopic test be applied to materials suspected of carcinogenic effects such as lubricating oil.

GEORGE RUKSTINAT

EPIDERMOID CARCINOMA OF THE HEAD AND NECK. RUPERT A. WILLIS, J. Path. & Bact. **33** 501, 1930

Epidermoid carcinoma of the head and neck frequently invades the internal jugular or other main cervical veins, producing an intravascular thrombus permeated by malignant cells, a condition present in twelve of the twenty unselected cases of the present series. Remote visceral metastases from craniocervical epidermoid cancer are by no means infrequent, and were present in ten of the twenty cases described, or (including a subsequent series) in seventeen of thirty-five cases. The origin of visceral deposits in these cases is invariably to be found in malignant penetration of the lumen of the main veins in the neck. Macroscopic pulmonary metastases frequently but not invariably develop following the liberation of malignant emboli from the cervical veins. The explanation of the absence of visible metastases in the lungs in cases presenting visceral deposits elsewhere is discussed. The liver is the most frequent site of development of systemic metastases, and as evidenced by the number of mitoses present hepatic tissue is a highly fertile soil for epidermoid cancer cell multiplication. Established visceral metastases frequently penetrate adjacent veins in a manner similar to that described in the neck, thus establishing new malignant embolic cycles. Penetration by a hepatic metastasis of branches of the portal vein in the liver results in further dissemination of malignant cells to other parts of the viscus, which in this way may become heavily sown with secondary growths. Penetration of a tributary of the portal vein by a metastasis in one of the organs in the area of portal drainage, e. g., the spleen, may also produce a further brood of hepatic deposits. Hepatic metastases may invade the hepatic veins, thus establishing a further embolic cycle to the lungs. The media of arteries and medullated nerves both exhibit decided freedom from malignant invasion.

AUTHORS' SUMMARY

VARIATIONS IN THE GROWTH OF THE JENSEN RAT SARCOMA AND THE INFLUENCE OF TECHNIQUE. H. CHAMBERS and G. M. SCOTT, J. Path. & Bact. **33** 553, 1930

Experiments are described which show that the transplanted Jensen rat sarcoma at the present time has in a pure breed stock many of the characteristics of a spontaneous malignant tumor. In 272 rats no tumor absorbed spontaneously, in a series of 52 rats, 86 per cent were successfully remodeled and metastases were found in a large number. The rate of growth has considerably increased. Rats have been bred relatively immune to Jensen rat sarcoma. The capacity of tumor cells to produce immunity varies with the condition of the tumor from which the grafts are taken. To obtain comparable results with the Jensen rat sarcoma the technique of transplantation needs careful and precise attention.

AUTHORS' SUMMARY

AN EARLY TAR CANCER OF THE RABBIT'S EAR WITH PENETRATION OF THE CANCER CELLS INTO THE BLOOD VESSELS. A. BABES, Bull. Assoc. franç. p. l'étude du cancer **19** 162, 1930

The internal surface of the ear of a female rabbit was painted with Roumanian tar, resulting in the appearance of a cancer within twenty days. The malignant disease was found on both sides of the painted ear. A biopsy revealed the presence of cancer in the circulation.

B. M. FRID

NEUROBLASTOMA OF THE FIRST BRANCH OF THE TRIGEMINUS W HACKEL,
Frankfurt Ztschr f Path 40 31, 1930

In a woman, aged 43, a tumor was found in the middle cranial fossa, situated close to the left internal carotid artery and the sinus cavernosus, in the region of the third branch of the trigeminus. A few small meningiomas of the dura were also found. The main tumor consisted of ganglion cells, which in part were degenerated, neuroblasts, some of which were arranged in the form of rosettes, and a few neurogonia. Nerve fibers were demonstrated between the neuroblasts and the groups of ganglion cells. Several areas of necrosis were encountered in the peripheral portion of the tumor. There were accumulations of lymphoid cells about the blood vessels. The first branch of the trigeminus, partially infiltrated with tumor cells, was found in the sections of the marginal portions of the tumor. In accordance with the classification of von Fischer (*Frankfurt Ztschr f Path* 28 663, 1922), this tumor is termed as an immature, infiltrating ganglioneuroma. A sympathetic heterotopia or remnants of a sympathetic anlage within the third branch of the trigeminus are regarded as the possible source of origin.

GROWTH OF THE ROUS SARCOMA E FRANKEL, Klin Wchnschr 9 1064, 1930

By the Willstätter method for the isolation of ferments and using aluminium hydroxide as absorbent, Frankel recovered the active substance from filtrates of the Rous sarcoma.

AUTHOR'S SUMMARY

PRIMARY MELANOBLASTOMA OF THE LIVER M BRANDT, Ztschr f Krebsforsch
31 254, 1930

Two cases of melanoblastoma are here reported, one certainly primary in the liver and limited to that organ, the other probably primary there, but with dissemination to the spleen, the submucosa of the upper jejunum and the lungs. In the first case aggregations of typical stellate Kupffer cells were found in otherwise uninvolved portions of the liver, and some scattered pigmented cells were present in the splenic sinuses.

H E EGGERS

Medicolegal Pathology

IDENTIFICATION OF ASSASSIN BY MICROSCOPE BALHAZARD, Ann de med leg
110 73, 1930

A man was shot with a revolver, the muzzle of which was held against the back of the head. The suspected murderer was identified by finding not only spots of human blood on the vest and trousers but also by finding on the vest bits of cerebellar tissue. The dried scales on the vest were soaked in salt solution for two hours and then embedded in paraffin and stained by Nissl's method.

CARBON MONOXIDE POISONING WITHOUT EXTINCTION OF FLAME UNDER
WASH BOILER F NAVILLE and C SOUTTER, Rev med de la Suisse Rom
50 336, 1930

The cause of four cases of fatal carbon monoxide poisoning under somewhat similar circumstances was investigated. In each case the victims were found in or near a room in which a washer had been left to boil over a gas burner. Blood tests showed 16.5, 16, 18 and 20 per cent, respectively, of carbon monoxide present. As there was no odor of fuel gas in the rooms, a search was made to discover the source of the gas. A simple experiment was made under the conditions that obtained in the four cases. This revealed that the carbon monoxide was formed immediately and not as a result of prolonged combustion. The steam from the boiler was in no way a contributing factor because, when the experiment was completed the water in the boiler was scarcely warm. Fuel gas is composed

essentially of hydrogen, hydrocarbons and carbon monoxide, the first two burn at a lower temperature than carbon monoxide. The gas flame comes in contact with the bottom of the washer filled with water, spreads out and cools. The larger the metallic surface and the amount of water, the lower the temperature of the flame. The hydrogen and hydrocarbons, which are highly combustible, burn completely into water and carbon dioxide, but some of the carbon monoxide does not and passes off into the air. Thus, rather than a close atmosphere, or a deficiency in the oxygen consumed by the flame, was the cause of the four deaths. In the apparent utter harmlessness of all the apparatus involved as well as in the lack of any characteristic odor to warn of the presence of carbon monoxide lies the unsuspected menace, of which the public should be promptly warned.

THE PATHOLOGIC ANATOMY OF SEPTIC ABORTION. K. LOWENTHAL, *Deutsche Ztschr f d ges gerichtl Med* **15** 265, 1930

The routes of infection after abortion are discussed on the basis of a study of fifteen cases. Emphasis is placed on an ascending suppurative process in the pelvic connective tissue and psoas muscle following perforation of the anterior wall of the cervix. Fatal infection, primarily a peritonitis, may follow abortion but be due to the rupture of an existing suppurative focus. To detect minute perforations, microscopic examination may be necessary.

CONCERNING THE DETERMINATION OF THE TIME OF DEATH OF HUMAN BODIES. H. MERKLI, *Deutsche Ztschr f d ges gerichtl Med* **15** 285, 1930

This is a report at the meeting of Deutsches Gesellschaft für gerichtliche und soziale Medizin, September, 1929, and the various phenomenon that tend to throw light on the question of the time of death are considered systematically. The details should be studied in the original. The special significance of the earliest possible observations on the dead body itself and its surroundings is emphasized.

THE EFFECT OF IRONING AND MANGING ON THE DEMONSTRATION OF BLOOD SPOTS ON CLOTH. E. SCHULZ, *Deutsche Ztschr f d ges gerichtl Med* **15** 343, 1930

Ironing and mangling reduce the solubility of blood coloring matter and proteins in blood stains. Potassium hydroxide requires a comparatively long time to extract the coloring matter from blood stains after ironing, and the demonstration of hemin crystals from blood spots that have been ironed may fail. The action of the heat in ironing does not completely hinder the precipitin reaction, but prolonged extraction with salt solution may be necessary on account of the reduced solubility of the serum proteins.

THE ASPIRATION AND DEGLUTITION OF BRAIN TISSUE AS EVIDENCE OF THE VITAL OCCURRENCE OF SEVERE INJURIES. K. WALCHER, *Deutsche Ztschr f d ges gerichtl Med* **15** 398, 1930

In severe injuries with extensive crushing of tissues it may be difficult if not impossible to decide whether the injury occurred during life or after death. Walcher describes four instances of extensive injuries to the head, three of which were due to motor trucks, in which pieces of brain tissue were aspirated deeply into the lungs and in two of the cases also swallowed. The aspiration and swallowing of brain tissue are regarded as showing clearly that the injuries in these cases were received during life.

DEATH BY STRANGULATION. LOCHTE, *Deutsche Ztschr f d ges gerichtl Med* **15** 419, 1930

This article is a detailed discussion of the importance of sinus caroticus (Hering) in cases of force on the neck (hanging, strangulation, boxing etc.) in

which the autopsy observations appear to be negative. The person dies suddenly without passing through all the phases of asphyxiation (unconsciousness, dyspnea, convulsions, etc.) because of a reflex action, probably of the laryngeal nerve (laryngeal shock), on the heart. The compression of the sinus caroticus produces a ventricular fibrillation, and death may follow rapidly. Death occurring in persons in whom compression of the neck was negligible (of brief duration, slight force, etc.) is thus explained. In instances of strangulation, one may, therefore, meet two types of death: one due to a gradually ensuing asphyxiation accompanied by hemorrhages, or a shocklike death. The latter cases are of particular medicolegal importance as the results of the postmortem examination may be negative, or in other words, that it suggests sudden death from natural causes.

E. L. MILOSLAVICH

MEDICOLEGAL SIGNIFICANCE OF DEATH FOLLOWING INJURIES IN SPORT

WALTER CREUTZ, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **15** 433, 1930

Sudden death after a boxing match is often due to subdural hemorrhage, apparently because of the tearing of delicate pial veins. In one case, death occurred three months after the fight, and a recurrent internal hemorrhagic pachymeningitis was found. The skull may be fractured by a blow from a fist (Braine and Ravina). Trauma of the skull and brain were observed also in football players, who not uncommonly suffer fatal injuries to the spine. Traumatic laryngeal shock (sinus caroticus) with sudden death, and traumatic edema of the glottis are also considered. Blunt injuries to the abdomen (in football play, wrestling) may produce internal hemorrhage, peritonitis (transmigration of intestinal bacteria due to injury to the bowel) or tearing of the bowel. Injuries to the liver, spleen and kidney during athletics are also mentioned, the last as occurring particularly in football players. The legal question of contributory negligence, according to the German criminal law, is discussed.

E. L. MILOSLAVICH

PERFORATION OF A SOLITARY ULCER OF THE INTESTINE

M. SAKORRAPHOS and B. PHOTAKIS, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **15** 455, 1930

This article is a description of a perforating ulcer of the ascending colon in a man, aged 64, and of a similar single ulcer in the jejunum of a man, aged 58. This ulcerous process in each case seems to have resulted from a necrotic infarct of the intestinal wall, since the ulcer was irregularly shaped and showed ragged edges.

E. L. MILOSLAVICH

NITROBENZENE POISONING AND HEMORRHAGIC ENCEPHALITIS

EDUARD GUNTZ, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **15** 461, 1930

A woman, aged 25, took nitrobenzene to induce menstruation. Soon after, an anesthesia-like unconsciousness followed, as a result of the action of the benzene, from which the patient recovered the next day. Alarming symptoms—cyanosis, dyspnea and disintegration of the blood (icterus)—gradually set in. Necropsy disclosed clotted blood in the veins and arteries because of a general capillary thrombosis, and a diffuse hemorrhagic encephalitis ascribed to toxic damage to the vessels.

E. L. MILOSLAVICH

DETERMINATION OF BLOOD GROUPS IN BLOOD SPOTS IN CRIMINAL CASES

K. FUJIWARA, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **15** 470, 1930

Three cases are described in which the determination of the blood groups of spots of blood on the clothing of persons suspected of crime gave valuable and significant results. In the fourth case, the determination of the group of seminal spots proved of value.

Society Transactions

PATHOLOGICAL SOCIETY OF PHILADELPHIA

Annual Gross Lecture Nov 13 1930

BALDWIN LUCKI, M.D. *President, in the Chair*

EXPERIMENTAL CANCER (SUMMARY) WILLIAM H. WOGIOM

A number of factors once thought to be responsible for malignant disease such as diet, soil and climate, have been gradually eliminated, and of them all only chronic irritation now seems significant.

The connection between malignant disease and chronic irritation had been suspected for years purely on observational grounds, and recent experimental work has greatly strengthened the presumption. Yet chronic irritation alone cannot be the sole cause, for some of the most irritating substances are devoid of carcinogenic activity, while less irritating ones, like tar, produce cancer readily in certain families of animals but not in others. It is evident that between the tissue and the irritant there is some adaptation of a delicacy hitherto unsuspected, and of which nothing is known, that is essential to the production of malignant growth.

Neither morphology nor chemistry has yet disclosed any characteristic difference between the cancer cell and other vigorously proliferating elements.

Though the subject of immunity to transplantable neoplasms has been eagerly investigated for thirty years, it has yielded no information that could possibly be of the slightest practical value at the present time. It is hardly necessary to state that no specific test or method of treatment has been devised so far, and that except for the alleviating and occasionally curative effect of radiotherapy, surgical intervention remains our only hope.

Nevertheless, there is no reason to despair, for more accurate knowledge has been gathered during the past thirty years of experimentation than was accumulated throughout the preceding thirty centuries of observation.

Dec 11, 1930

BALDWIN LUCKI, M.D., *President, in the Chair*

SCIENTIFIC MICROSCOPY MAN POSER

In scientific microscopy certain optical laws must be fulfilled in order to avoid false images caused by diffraction effects producing more or less optical illusions as compared with the real structure of a microscopic object. These optical laws are well defined in the report of the research work carried on by the late Professor Abbe, and it was the aim of Dr. Poser to discuss briefly the vital points pertaining to this investigation.

1 A homogeneous source of light is an essential factor in reliable microscopy, and the method of illumination must be adapted to suit the microscopic object under investigation.

2 In order to determine the resolution of an optical system of a microscope, the magnification is only a secondary factor, but the numerical aperture of the microscope objective is directly responsible for the resolution of the minute

details of the object. This is explained by the fact that a microscopic image consists of two kinds of images: (1) the image formed by the dioptric beam, which refers chiefly to the contour of the object, (2) and that of the more minute details in the structure of a microscopic object, which are rendered visible by means of the diffracted light beam caused by the object itself.

3 The term "aperture" of a microscope system is applicable only when dry objectives are involved. Regarding the determination of the resolution of the microscope with oil-immersion systems, the numerical aperture will furnish the correct information as to the resolution. It is therefore advisable to employ universally for low or high power work with the microscope the term "numerical aperture" when determining the resolving power of the optical system of the microscope, since this term applies to both low and high power microscope objectives.

4 The wave length of light is another factor of importance, since light of the shorter wave length of light in the spectrum used for illumination has a direct bearing on the resolving power of the objective.

5 The full illuminating cone should always be employed with stained objects, such as bacteria and other minute organic substances, while a greater penetrating power of the microscope system is essential with tissues of considerable depth of the section. From this it follows that the numerical aperture of the illuminating cone must be somewhat restricted, and thus the resolving power of a given optical system will be more or less limited.

6 Maximum contrast of the object under the microscope and the surrounding area cannot always be obtained with the staining of the object. A study of desirable light filters is therefore indicated in order to illuminate with light representing different color bands of the spectrum so chosen that the color of light selected for illumination in a given case neutralizes or absorbs the color of the staining solution and thus makes the object appear dark on a light background with direct illumination.

7 To examine living objects with dark ground illumination will be found useful in many cases in which living objects are to be investigated, and the best results are always obtained when light cones of extreme numerical aperture with the central beam cut out by an opaque stop of the desired dimension are used for the illumination of the object, with this kind of examination, the rule should be that the central stop and illuminating cone are so chosen that no direct light enters the objective.

8 When examining objects under the microscope with ultraviolet light, interesting results are obtained in all cases in which the medium in which the object is mounted or embedded does not absorb the ultraviolet light.

9 A given resolving power of an objective can almost be doubled when ultraviolet light of the shorter wave lengths is used for illumination, but such microscope lenses must then be made of quartz instead of glass, owing to the latter being more or less opaque to ultraviolet light of the shorter wave length.

10 When illuminated with ultraviolet light, objects showing fluorescence, luminescence or phosphorescence present an interesting study when examined in this manner particularly in cases in which living specimens come into consideration.

Book Reviews

LABORATORY MEDICINE A GUIDE FOR STUDENTS AND PRACTITIONERS By DANIEL NICHOLSON, M.D., Member of the Royal College of Physicians, London, Assistant Professor of Pathology, University of Manitoba, Assistant in Pathology, Winnipeg General Hospital Cloth Price, \$6, net Pp 437, with 108 engravings and 1 colored plate Philadelphia Lea & Febiger, 1930

The object of this book is to describe and interpret diagnostic laboratory tests and procedures. The first few pages outline briefly the tests that are indicated under various general conditions and are followed by chapters on the various tests of the blood, exudates and puncture fluids, sputum, cerebrospinal fluid, gastric and duodenal contents, urine and feces, on cutaneous tests, reactions of immunity and miscellaneous examinations (basal metabolism, biopsy, poisons), and finally on laboratory equipment. The book contains a great deal of useful information for the physician as well as for the clinical pathologist. On the inside front cover are given important normal standards. The author does not consider the details of the microscopic examination of tissues for diagnostic purposes. The statement on page 114, that Hodgkin's disease "is probably caused by the avian tubercle bacillus," seems at least premature. On page 195, ricinoleated antigen is listed as of proved value in protecting against scarlet fever, but its value is far from proved. Under examination of the skin for fungous disease (p. 335) there is no mention of blastomycosis or sporotrichosis. Chapter 12 on reactions of immunity, is valuable, in the next edition it should be revised with great care and enlarged to include the agglutination and Wassermann tests, which are now described in another chapter. Kahn's test and also agglutination tests for tularemia and brucellosis are not even mentioned. The description of vaccination against smallpox and the subsequent reactions is excellent. The statements about the diagnosis of infantile paralysis in the preparalytic stage, in which examination of the spinal fluid is so important, should be elaborated, and the method of injecting convalescent serum brought to date. By perfecting himself in the tests and procedures of known value in the diagnosis, prevention and treatment of infectious diseases the physician and clinical pathologist can greatly increase their usefulness.

A COMPILATION OF CULTURE MEDIA FOR THE CULTIVATION OF MICRO-ORGANISMS By MAX LEVINE and H. W. SCHÖNHEIM Cloth Price, \$15 Pp 969, with 7,000 formulas and four indexes Baltimore Williams & Wilkins Company, 1930

This compilation of culture mediums has been "prepared at the request of the Society of American Bacteriologists and financed by a grant from the Digestive Ferments Company, Detroit, Mich." Seven thousand formulas have been grouped into approximately 2,500 mediums, the constituents, preparation and use of which are described. The mediums are numbered consecutively but subdivided into 7 groups according to their physical states. For each group there is a key by means of which the individual mediums may be located. There are several indexes: medium name index, constituents index, which lists every medium in which a particular substance is used, an author index, a use index, listing the mediums "for which a specific use was indicated in the original article reviewed" and, finally, the list of references. In the constituents index are long lists of numbers of mediums containing substances in frequent use, e. g., calcium chloride, dextrose, glycerol, magnesium sulphate, potassium phosphate and sodium chloride. It is not clear what value such lists can have, but there is no question about the value of

the book as a whole. An enormous amount of useful information in bacteriologic work has been collected and indexed. The entire experience in the making of mediums since Koch's day is summarized. The originators and authors of the book deserve high credit.

J. GEORGE ADAMI. Sometime Strathcona Professor of Pathology McGill University, Montreal. A Memoir. By Marie Adami together with contributions from others, his friends, and an Introduction by Sir Humphry Rolleston Bart, G C V O, K C B, M D. Price, \$3.50. Pp 179. New York: Richard R. Smith, Inc., 1930.

American pathologists and physicians know J. George Adami best from his work and influence while professor of pathology (1892-1914) in McGill University. Many of them were deeply impressed by his philosophical articles on inflammation (1896) and on inheritance and disease (1907), as well as by his emphasis on pathology as a branch of biologic science and his activities in enforcing its bearings on medical practice and public health. He was, in fact, one of the most influential leaders in medicine on this side of the Atlantic when the World War called him back to England. The memoir, written by his widow but supplemented by contributions from fellow-workers and by a bibliography of his printed works, deals successively with his life and early work in Cambridge, with his Canadian period, his services during the war and his efficient activities as vice-chancellor of the University of Liverpool. A many-sided and charming personality stands forth clearly. The diminishing band of Adami's contemporaries and his pupils will read the memoir with grateful interest. As a worthy and appropriate record of "an exceptionally gifted leader in pathological and general education" it will have a wide appeal.

Books Received

MOLDS, YEASTS, AND ACTINOMYCETES A HANDBOOK FOR STUDENTS OF BACTERIOLOGY By Arthur T. Henrici, M.D., Professor of Bacteriology, University of Minnesota Price, Cloth, \$3.50 net Pp 296, with 100 illustrations New York John Wiley & Sons, Inc., 1930

MEDICAL BIOMETRY AND STATISTICS By Raymond Pearl, Ph.D., Sc.D., LL.D., Professor of Biology in the School of Hygiene and Public Health, and in the Medical School, Johns Hopkins University, Baltimore Edition 2 Price, cloth, \$5.50 Pp 459 Philadelphia W. B. Saunders Company, 1930

UEBER DAS PROBLEM DER BOSARTIGEN GLSCHWULSTE EINE EXPERIMENTELLE UND THEORETISCHE UNTERSUCHUNG Von Professor Dr. Lothar Heidenhain, in Worms Volume 2 Royal quarto Price, unbound, 42 marks, bound, 47.50 marks Pp 207, with 229 illustrations Berlin Julius Springer, 1930

THE MOVEMENTS OF THE EYES IN READING Medical Research Council Special Report Series, no 148 By M. D. Vernon Price, 9 pence net Pp 45 London His Majesty's Stationery Office, 1930

TECHNIQUES HISTOLOGIQUES DE NEUROPATHOLOGIE Par Ivan Bertrand, D'écateur à l'École pratique des Hautes Études, Chef de Laboratoire de la Clinique Neurologique de la Salpêtrière Préface du Professeur G. Guillaumin Price, 50 francs Pp 376 Paris Masson et Cie, 1930

NOSOGRAPHY THE EVOLUTION OF CLINICAL MEDICINE IN MODERN TIMES By Knud Faber, M.D., LL.D., Professor of Internal Medicine, University of Copenhagen With an Introductory Note by Rufus Cole, M.D., Director of Hospital, Rockefeller Institute Edition 2 Price, \$3.75 Pp 222, with 22 illustrations New York Paul B. Hoeber, Inc., 1930

METHODS AND PROBLEMS OF MEDICAL EDUCATION (EIGHTEENTH SERIES) New York The Rockefeller Foundation, 1930

ANNUAL MEDICAL REPORT OF THE CHICAGO TUBERCULOSIS INSTITUTE AND THE EDWARD SANATORIUM, 1929-1930

GEWEBSPROLIFERATION UND SAUREBASISGLEICHGEWICHT Von Dr. Rudolf Balint, O. O. Universitäts-Professor, Direktor der I. Medizinischen Klinik der Pázmány Péter-Universität in Budapest und Dr. Stefan Weiss Assistent der I. Medizinischen Klinik der Pázmány Péter-Universität in Budapest Mit einem Vorwort von Baron A. von Koranyi O. O. Universitäts-Professor Direktor der III. Medizinischen Klinik der Pázmány Péter-Universität in Budapest Price, unbound, 16.80 marks, bound, 18.40 marks Pp 209, with 59 illustrations Berlin and Vienna Julius Springer, 1930

THE ENTEROCHROMO-ARGENTAFFIN CELLS*

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The rôle of chromo-argentaffin cells in inflammatory processes has not been defined. A histologic investigation was undertaken with this end in view, with especial reference to the part played by the argentaffin cells in acute, subacute and chronic inflammations of the intestinal tract, in particular of the appendix. While it seems conclusive that the argentaffin cells give rise to the carcinoids of the intestinal tract, no definite conclusion has been reached with regard to their significance in inflammatory processes.

LITERATURE

Among the epithelial cells of the gastro-intestinal mucosa, there are a variety of granular epithelial elements of which the morphology, origin, function and pathologic significance have been of much interest since their first description by Paneth¹ in 1888 and Bizzozzero² in 1892. Somewhat later, Trautmann³ and others verified the investigations of Paneth, and spoke of these cells as the "granule cells of Paneth."

Kultschitzky⁴ observed other granular cells in the intestinal mucosa, the morphology and staining properties of which were unlike that of the "granule cells of Paneth." With Ehrlich-Biondi stain (acid fuchsin, orange and methyl green), the granules of the cytoplasm were colored red, and therefore he designated them as the "cells with acidophil granules." He noticed that the granules always occupied the basilar portion of the cell.

Schmidt⁵ found cells similar to those discovered by Kultschitzky

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1 Paneth, J. Ueber die sezernierenden Zellen des Dunndarmepithels, *Arch f mikr Anat* **31** 113, 1888.

2 Bizzozzero, G. Ueber die Schlauchformigen Drusen des Magen-Darmkanals und die Beziehung ihres Epithels zu dem Oberflachenepithel der Schleimhaut, *Arch f mikr Anat* **40** 325, 1892.

3 Trautmann, G. Zur Kenntnis der Panethschen Kornzellen bei den Säugetieren, *Virchows Arch f path Anat* **151** 261, 1897.

4 Kultschitzky, N. Zur Frage über den Bau des Darmkanals, *Arch f mikr Anat* **49** 7, 1897.

5 Schmidt, J. E. Beiträge zur normalen und pathologischen Histologie Zellarten der Schleimhaut des menschlichen Darmkanals, *Arch f mikr Anat* **66** 12, 1905.

in the crypts of Lieberkuhn, and was the first to give a complete description of their morphologic characteristics. When the tissues were fixed in Muller's solution plus formaldehyde, the basal portion of the cell stained intensely yellow. He found that the nuclei of argentaffin cells were larger than the nuclei of the adjacent cells of the glands of Lieberkuhn. Schmidt named these cells "yellow cells." He also noticed similar cells in the underlying network of nerves and concluded that these periglandular "yellow cells" migrated from the glands of Lieberkuhn.

Ciaccio,⁶ studying independently, found such cells in the stomach and the duodenum in the guinea-pig and the dog. He demonstrated vacuoles in the granular portions of the cytoplasm.

For a time the interest aroused by the observations of Kultschitzky and Schmidt subsided, but attention was again awakened when Huebschmann,⁷ while studying the carcinoids of the appendix, noticed cells with morphologic and staining characteristics similar to those of the cells of Kultschitzky and Schmidt. Further investigation convinced him that the carcinoids originated from these cells and from the "granule cells of Paneth."

Masson⁸ also examined carcinoids, he found that they were composed mainly of cells corresponding to those described by Kultschitzky and Schmidt. He demonstrated the reducing property of the granules to ammoniacal silver, and as a consequence of a predilection for silver, he named the cells "argentaffin cells." Masson was convinced that the argentaffin cells were the same as the cells of Kultschitzky, Schmidt and Ciaccio.

Recent investigators, Cordier,⁹ Forbus,¹⁰ Hamperl,¹¹ Eros,¹² Sprafke¹³ and others, verified the morphologic observations of Masson, but they disagreed with him as well as among themselves, concerning the origin, function and pathologic significance of these cells.

6 Ciaccio, C. Sur une nouvelle espece cellulaire dans les glands Lieberkuhn, *Compt rend Soc de biol* **60** 76, 1906.

7 Huebschmann, P. Sur le carcinome primitive de l'appendice vermiculaire, *Rev med de la Suisse Rom* **30** 317, 1910.

8 Masson, P. Tumeurs endocrines de l'appendice, *Presse med* **22** 25, 1914.

9 Cordier, R. Contribution a l'etude de Ciaccio-Masson et la cellule de Paneth, *Compt rend Soc de biol* **88** 1227, 1923.

10 Forbus, W. D. Argentaffin Tumors of the Appendix and Small Intestine, *Bull Johns Hopkins Hosp* **37** 130, 1925.

11 Hamperl, H. Ueber die gelben (chromaffinen) Zellen in gesunden und kranken Magendarmschlauch, *Virchows Arch f path Anat* **266** 509, 1927.

12 Eros, G. Ueber die argentaffinen Zellen der Schleimhaut des Magen und Darmtraktes, *Frankfurt Ztschr f Path* **36** 402, 1928.

13 Sprafke, H. Untersuchungen uber die argentaffinen Zellen in der Schleimhaut des Wurmfortsatzes und ihre Beziehungen zur Entstehung der sogenannten Karzinoide, *Frankfurt Ztschr f Path* **35** 302, 1927.

Many hypotheses have been formulated to account for the origin of the enterochromo-argentaffin cells, yet the genesis of these cells still remains obscure

The early investigators made only feeble attempts toward investigative proof, but later researches have thrown some light on the histogenesis of these granule cells. Masson's¹⁴ embryologic studies led him to believe that the chromo-argentaffin cells are of entodermic origin. He demonstrated their appearance in the intestinal mucosa of man about the fourth month of fetal life. Parat confirmed Masson's observations, but Kull,¹⁵ who studied the cells in the chick embryo by the mitochondrial method (he did not use ammoniacal silver), reported that the chromaffin cells originated from mesenchyme cells that had invaded the epithelium. Masson refuted Kull's report by contending that the mitochondria of the connective tissue and the chromaffin granules of the chromo-argentaffin cells differ widely in both size and staining reactions.

Danisch¹⁶ showed that the chromo-argentaffin cells arise from the celiac ganglion and migrate into the gastro-intestinal mucosa about the fourth month of fetal life. He found these cells in the submucosa in the tenth week of embryonal life, but he was unable to demonstrate argentaffin cells in embryos of six weeks. Masson⁸ urged the rejection of Danisch's observations because the latter had used macerated material and had stained his sections by Agdhu's silver technic. Agdhu's silver technic colors certain chromaffin cells of the sympathetic paraganglia, but does not color the argentaffin cells specifically.

As a result of two pathologic observations, Masson stressed the entodermic origin. He found many argentaffin cells in regenerating epithelium of chronic gastritis, and argentaffin cells are always mixed with cylindric cells in the carcinoids of the intestinal tract.

Hampeil¹¹ did not think that the argentaffin cells belong to the chromaffin system, he attributed their origin to a faulty differentiation during the regeneration of the epithelium after inflammation.

Many workers who found similar cells in the pancreatic islets, suprarenal glands and hypophysis concluded that these cells belong to the chromaffin system. Tang¹⁷ expressed the belief that the cells might be a type belonging to the "granule cells of Paneth."

14 Masson and Berger. Sur un nouveau mode de secretion interne la neurocrinie. *Compt rend Acad de sc* **176** 1748, 1923

15 Kull, H. Die chromaffinen Zellen des Verdauungstraktes. *Ztschr f mikr anat Forschung* **2** 163, 1925

16 Danisch, F. Zur Histogenese der sogenannten Appendixkarzinome, *Beitr z path anat u z allg Path* **72** 687, 1923-1924

17 Tang, E. H. Ueber die Panethschen Zellen sowie die gelben Zellen des Duodenums beim Schwein und den anderen Vierbeltieren, *Arch f mikr Anat* **96** 182, 1922

Block claimed that the "granule cells of Paneth" aided the digestion of milk. Klein¹⁸ suspected that the granules of Paneth's cells were zymogen granules. Zimmerman¹⁹ maintained that they were serous cells. Bensely considered them as serous zymogen cells, and Macallum as prozymogen cells. Bizzozero² contended that they were young mucin cells.

Kultschitzky⁴ was certain that the cells possessed some functional attributes in the process of digestion. He noticed a certain number of these cells in his normal dogs. When a dog was subjected to a diet wholly of meat, Kultschitzky found that the number of argentaffin cells increased, however, when he starved the dogs and cleared the gastro-intestinal tract with magnesium sulphate, he was unable to demonstrate a single argentaffin cell throughout the entire gastro-intestinal tract.

Schmidt⁵ maintained that the argentaffin cells possess some nervous functional element. Ciaccio,⁶ because of their chromaffinity, hypothesizes that these cells might produce epinephrine which is poured into the gastro-intestinal tract. However, the marked and almost specific reaction of these cells to ammoniacal silver suggests that the substance secreted and true epinephrine are not similar.

Masson,⁸ in his early papers, contended that the argentaffin cells possess an endocrine function. In his later works, while studying obliterated appendixes, Masson observed certain minute tumors known as neuromas or neuromas. In the center of these neuromas, he always demonstrated argentaffin cells. It is certain that neuromas originate from the periglandular plexus. In normal and inflamed appendixes, he noticed a budding of the glands of Lieberkuhn and the pushing out of argentaffin cells from a ruptured basement membrane. Masson was able to find more periglandular argentaffin cells in appendixes with pathologic histories. He also found that wherever the periglandular argentaffin cells were abundant, the periglandular nerves were hypertrophied and had even undergone hyperplasia. Thus, by correlating the glandular and periglandular argentaffin cells with the nervous hypertrophy and hyperplasia, Masson concluded that the neuromatosis of certain appendixes was influenced by the extraglandular argentaffin cells.

In short, Masson's explanation is that the periglandular argentaffin cells are the glandular argentaffin cells that have migrated from the crypts. Whether the periglandular cells possess some nutritive or irritative influence on the periglandular plexus to cause them to grow is not definitely known. However, Masson's work proved that the existence of these neuromas depends on the presence of the argentaffin

18 Klein, S. On the Nature of the Granule Cells of Paneth in the Intestinal Glands of Mammals, *Am J Anat* **5** 315, 1906.

19 Zimmerman, K. W. Beiträge zur Kenntnis einiger Drüsen und Epithelien, *Arch f mikr Anat* **52** 552, 1898.

cells When the argentaffin cells degenerate, the neuromas also degenerate Masson²⁰ thought it fitting to designate the activity of the periglandular argentaffin cells as "a neurocrine function," because these cells are able to promote and maintain a well nourished and growing periglandular plexus

According to Kull,¹⁵ the argentaffin cells possess two Golgi processes, one apical and the other basal, but Cowdry²¹ stated that the Golgi apparatus is connected with the pole of discharge Furthermore, in certain carcinoids there are cavities filled with a homogeneous colloid liquid and bordered by argentaffin cells This might indicate that the argentaffin cell secretes something from its apical pole From the preceding observations one may conclude that these cells have an exocrine function However, Masson said, "This does not exclude a concomitant endocrine function The liver cells normally exhibit polarities external and internal, the pancreatic cell exhibits them successively"

Cordier⁹ waived the belief that the argentaffin cells have an endocrine function, but he was certain that they have an exocrine function, for after an injection of pilocarpine the granularity of the cells lessened or disappeared altogether Masson did not deny the granular diminution after the injection of pilocarpine, but he maintained that Cordier had been unable to demonstrate in which direction the product that results from the destruction of the argentaffin granules is excreted

Embryologic investigations convinced Danisch¹⁶ that since the argentaffin cells originate from the solar plexus they must possess some paraganglionic function

I have observed that as long as the chromo-argentaffin cells are in contact with the basement membrane of Lieberkuhn's glands, the granules are always aggregated at the base Such basal massing indicates, as Masson said, an "endotopic polarization," and thus supports the logical conclusion that these cells possess an endocrine function Entz long ago proclaimed the hypothesis that in every organ, as well as in the gastro-intestinal tract, endocrine cells must exist Perhaps the chromo-argentaffin cells are the cells of Entz's hypothesis

MATERIAL USED FOR STUDY

At the Milwaukee County Hospital, tissues from forty-five necropsies and sixty-six appendices removed at operation were studied The necropsy material consisted of all portions of the gastro-intestinal tract, including the appendix, pancreas, suprarenal glands, paraganglionic tissue and the hypophysis The duodenum of the rabbit and that of the guinea-pig were also studied

20 Masson, P Carcinoids (Argentaffine-Cell Tumors) and Nerve Hyperplasia of the Appendicular Mucosa, *Am J Path* 4 181, 1928

21 Cowdry, R The Reticular Material as an Indicator of the Physiologic Reversal in Secretory Polarity in Thyroid Cells of Guinea-Pig, *Am J Anat* 30 25, 1922

Five hundred and forty serial slides were prepared. Each slide contained from ten to forty sections, and the following were considered: the normality, the pathologic appearances and the postmortem changes of the tissues, the proportional nervous, lymphoid and glandular character of the appendices, and the morphology, staining, situation and distribution of the argentaffin cells.

THE SILVER STAINING METHOD

With the Ehrlich-Biondi-Heidenham method, the granules stained red, with Muller's solution plus formaldehyde yellow, with Masson's method, black, and with basic blues, greenish-blue. The chromo-argentaffin cells were demonstrated best by Masson's method, which is as follows:

- 1 Fix tissue (fresh tissue, if possible) in Bouin's solution three days (Bouin's solution: formaldehyde solution, 10, trinitrophenol, 30, acetic acid, 2)
- 2 Transfer to neutral solution of formaldehyde for from one to two months
- 3 Cut section from 1 to 2 mm thick
- 4 Wash in distilled water from twelve to twenty-four hours
- 5 Transfer to ammonia water for from twelve to twenty-four hours (500 cc of distilled water with 2 drops of ammonia)
- 6 Place in Fontana solution half diluted for six days, excluding all light
- 7 Place in reduction fluid for from six to eight hours (formaldehyde solution, 5, water, 50, pyrogallol acid, 5)
- 8 Embed in paraffin

Most of the sections were stained by this method. The surgical department was supplied with small bottles containing Bouin's solution which were labeled 'for appendices and other gastro-intestinal tissues'. Thus it was assured that fresh tissue was placed in a very efficient fixing solution. About thirty of the appendices removed at operation were fixed by this method, the remaining thirty-six were sent to the laboratory in 10 per cent formaldehyde and then transferred into Bouin's solution. About 75 per cent of the necropsy material was placed directly in Bouin's solution, the remaining 25 per cent was first placed in 10 per cent formaldehyde and then transferred to Bouin's solution.

Silver is the most capricious stain for microscopic study. One is often at a loss to explain adequately the variability and the fluctuation of the same type of cells toward impregnation with silver. Unless one enforces a careful technique, the impregnation with silver yields many artefacts. Great care was taken in preparing the solutions, and strict attention was given to the reduction time. Sections that showed too much precipitation and thus manifested artefacts were discarded, even though they contained extraglandular argentaffin cells.

DISTRIBUTION OF THE ARGENTAFFIN CELLS

The enterochromo-argentaffin cells are distributed inconstantly throughout the entire gastro-intestinal tract. They are found singly or in pairs among the columnar cells of the stomach, duodenum and appendix. Occasionally, they may be demonstrated in the cardiac portion of the stomach and the large intestine. They are also found singly or in groups of from three to twenty-five cells (fig. 1) in the periglandular plexus of nerves, but cannot be demonstrated in the lymphoid tissue or in the external nerve plexus. Thus, two distinct classes should be considered: (1) glandular enterochromo-argentaffin

cells and (2) periglandular enterochromo-argentaffin cells. Silver-reducing cells that simulate the enterochromo-argentaffin cells were demonstrated in the islands of Langerhans of the pancreas and in the suprarenal cortex, hypophysis and paraganglionic tissue, but it was found that their staining and morphologic characteristics differ from the enterochromo-argentaffin cells. The argentaffin cells of the islands of

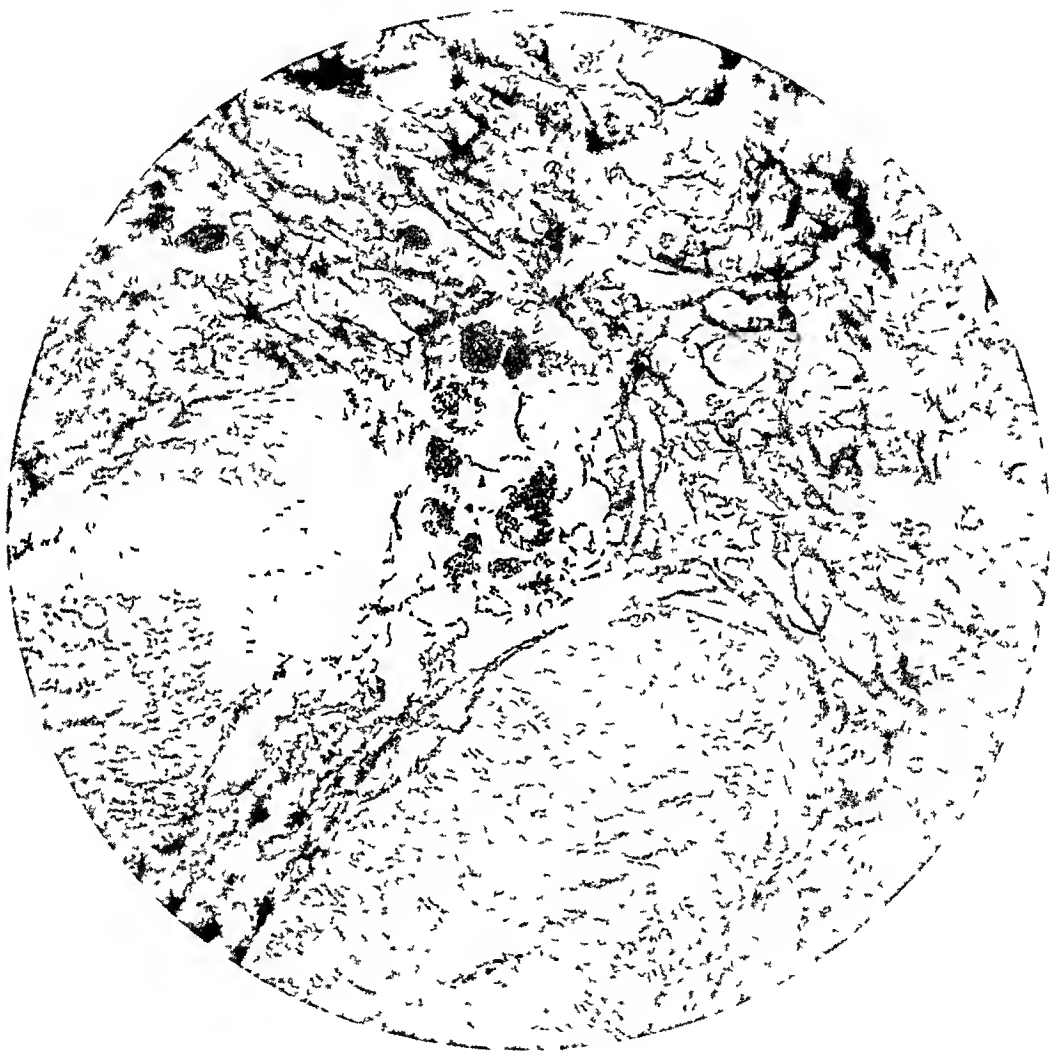


Fig 1—A group of eight periglandular argentaffin cells of the epithelial type observed in a section of the appendix. The light-staining nuclei are almost centrally located

Langerhans are smaller, and their nuclei are round, distinct and centrally located, they reduce silver very mildly. The argentaffin cells of the suprarenal glands contain fine granules distributed throughout the cytoplasm; the granules stain dark brown, and the nuclei are not as definite as those of the cells found in the islands of Langerhans. Nevertheless the argentaffin cells of the pancreatic islands and those

of the suprarenal gland are somewhat similar. The argentaffin cells of the two hypophyseal glands reduce silver to a greater degree than the cells of the suprarenal glands and the islands of Langerhans. The paraganglionic argentaffin cells reduce silver with almost as great intensity as do the argentaffin cells of the intestinal tract, however, they can be easily recognized by their processes.

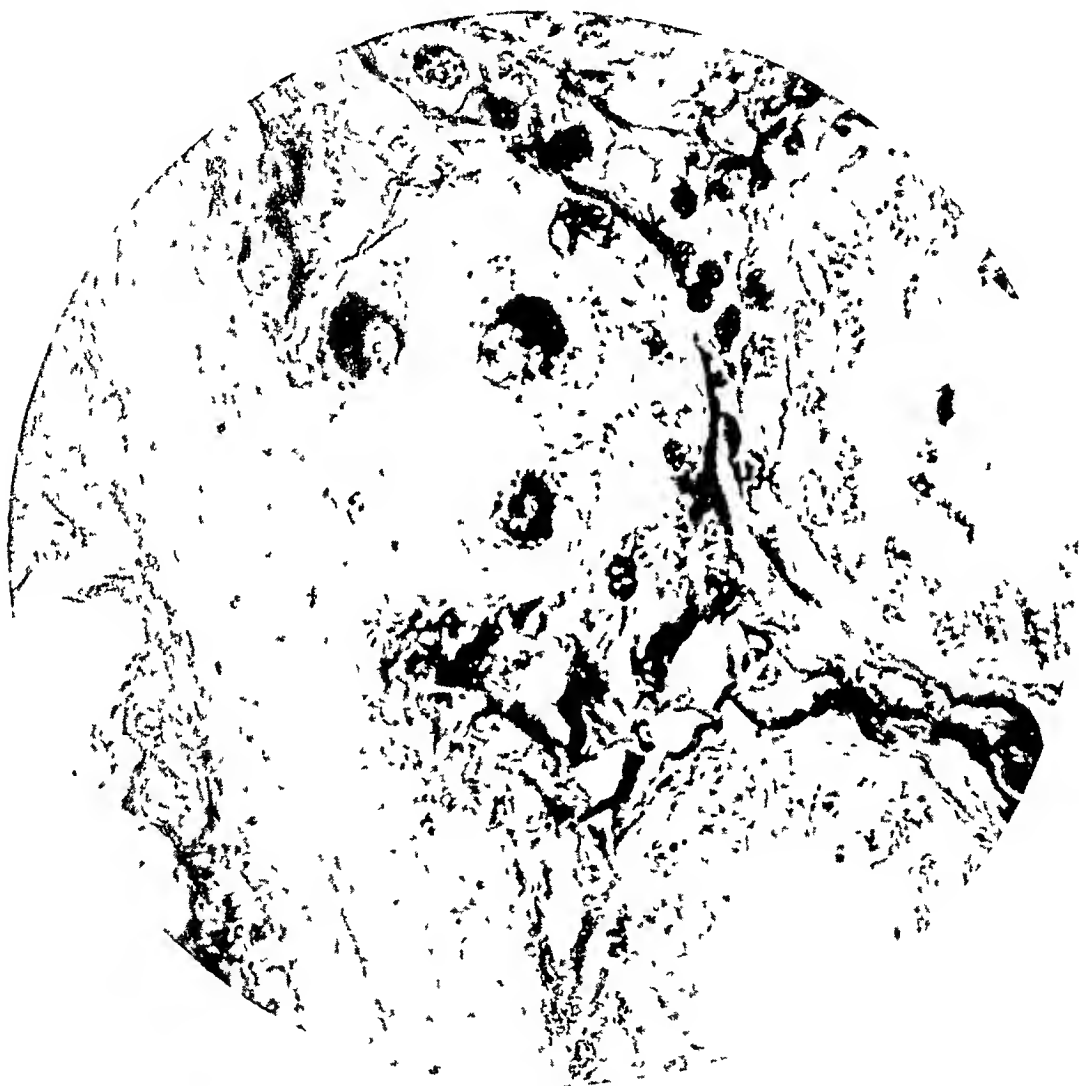


Fig 2—Three argentaffin cells in a transverse section of a gland of Lieberkuhn. The appendix was obtained at operation from a patient 7 years of age and showed subacute appendicitis.

GLANDULAR ENTEROCHROMO-ARGENTAFFIN CELLS

The glandular argentaffin cells are scattered among the cylindrical cells that line the gastro-intestinal tract. They are more abundant in the crypts of Lieberkuhn, where from one to twenty-eight argentaffin cells may be counted in 100 microns of tissue. From about 70 per cent to 90 per cent of these cells are found at the bottom of the crypts.

Masson gave the average as between five and ten cells per crypt. From one to three (fig 2), rarely four, argentaffin cells can be seen in the transverse sections of the glands of Lieberkuhn, the average being one or two cells. They are less frequent in the upper portions, but may be found as high as the tip of the villus.

The form of the glandular enterochromo-argentaffin cell is fairly constant. The cell may be conical (fig 3), pyramidal (fig 4) or flask-

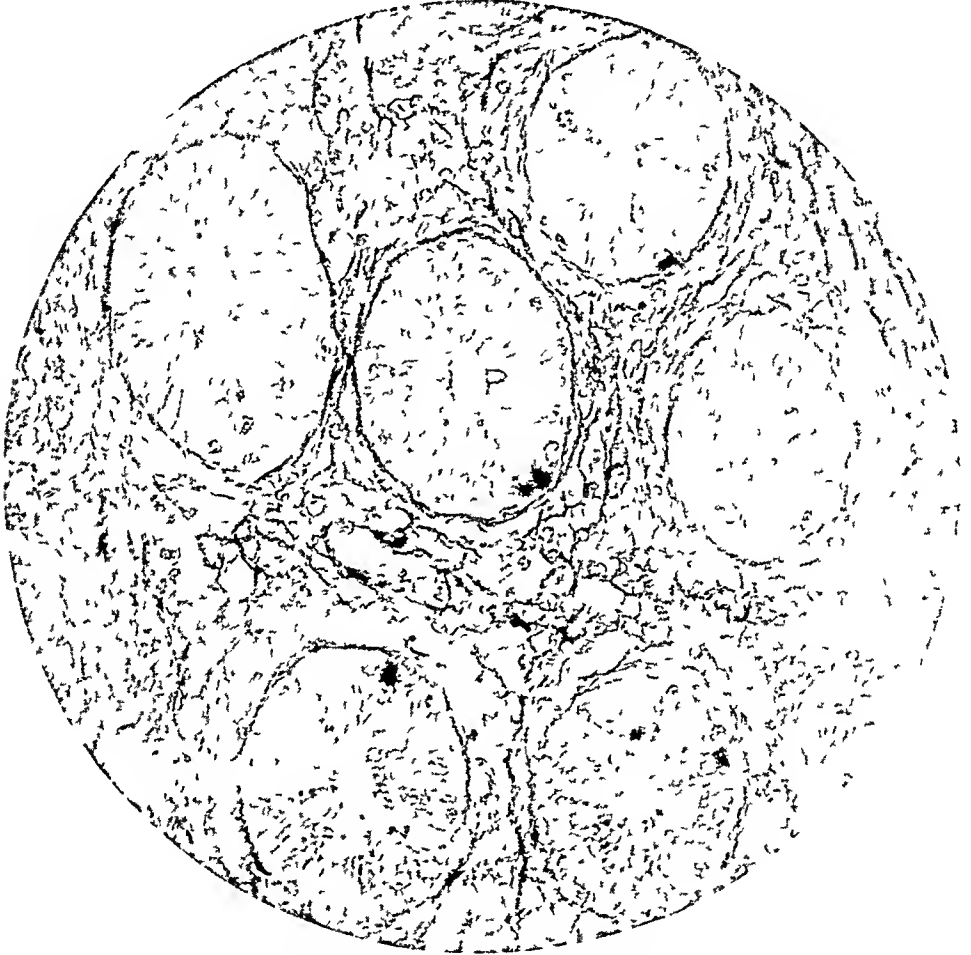


Fig 3—Five slender, conical glandular argentaffin cells. The nuclei contain very little chromatin granules. Many sections were prepared from this appendix, and no supranuclear granulations were found. The appendix was obtained at necropsy from a man 71 years of age.

shaped (fig 5). However, the size of the cell frequently varies. Much depends on the species and the region in which it is found. I have seen various sizes in the same section and even in the same gland. In comparison with the contiguous cylindric epithelial cells that line the glands of Lieberkuhn, it is usually shorter and wider (fig 4), but it may

be as tall and as narrow as the cylindric cells. Usually the apical portion is not seen to reach the lumen of the gland, and is lost among the cylindric cells, but occasionally the apex may be seen reaching the lumen (fig 5). The average size of the argentaffin cell is 16 microns in height and 9 microns in width, the cylindric cell is 20 microns high and 4 microns wide.

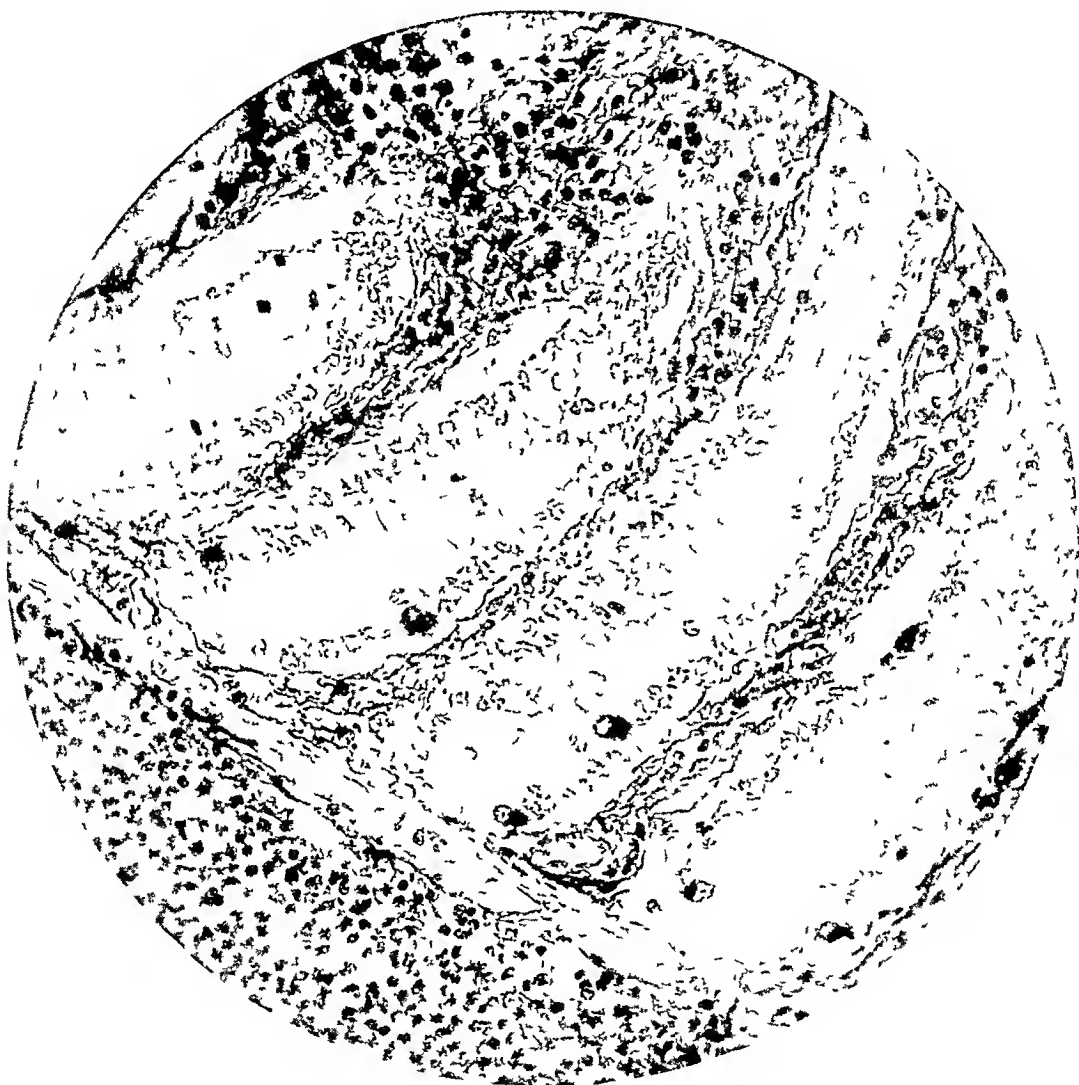


Fig 4—Seven pyramidal glandular enterochromo-argentaffin cells in an appendix obtained at autopsy from a 21 year old patient who died of lobar pneumonia.

Cytoplasm—The cytoplasm is clear and homogeneous and does not stain as well as the cytoplasm of the cylindric cells. The cytoplasm below the nucleus contains many granules. The presence of granules in the basal portion of the cytoplasm is constant, but their presence in the supranuclear region is very inconstant. Above the nucleus, they may be absent entirely, but frequently one finds a few fine granules scattered

in the vicinity of the upper pole of the nucleus (figs 4 and 5). More often they are found at the sides and the adjacent portions above the nucleus (fig 6), here the granules may be as numerous as in the basal pole of the cell. Occasionally, the entire cytoplasm is filled with argentaffin granules. When such a cell is found, it appears as a black pyramid-shaped object with a central light area, the nucleus (Masson's method).

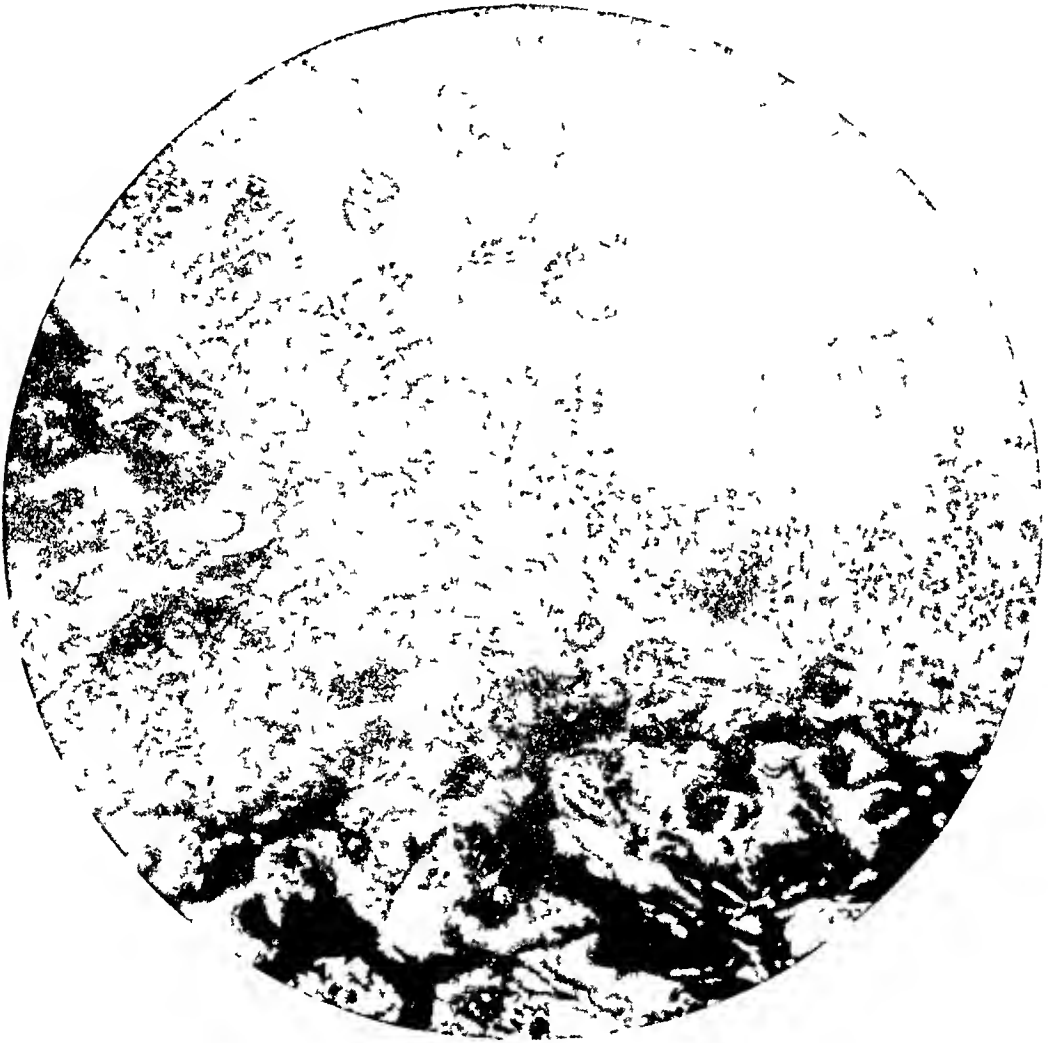


Fig 5—Two glandular argentaffin cells of the appendix. The one located in the right hand portion of the field is a flask-shaped cell the entire outline of which is plainly visible and the apical portion of which is seen to reach the lumen.

As the granules vary in quantity, so they also vary in size and staining characteristics. Much depends on the technic employed. Some granules do not reduce silver or rather reduce it sluggishly, but stain well with acid dyes, however, the great majority of the cells contain granules that reduce ammoniacal silver with marked intensity. This

inconstant reduction may be seen in the same section or even in the same crypt. Masson thought that the different sizes and the variable staining characteristics are due to the different evolutionary stages of the granules. The cytoplasm also contains a few vacuoles, which are usually located in the basal pole of the cell. These vacuoles are sometimes filled with doubly refractory lipoids and they stain with sudan III.

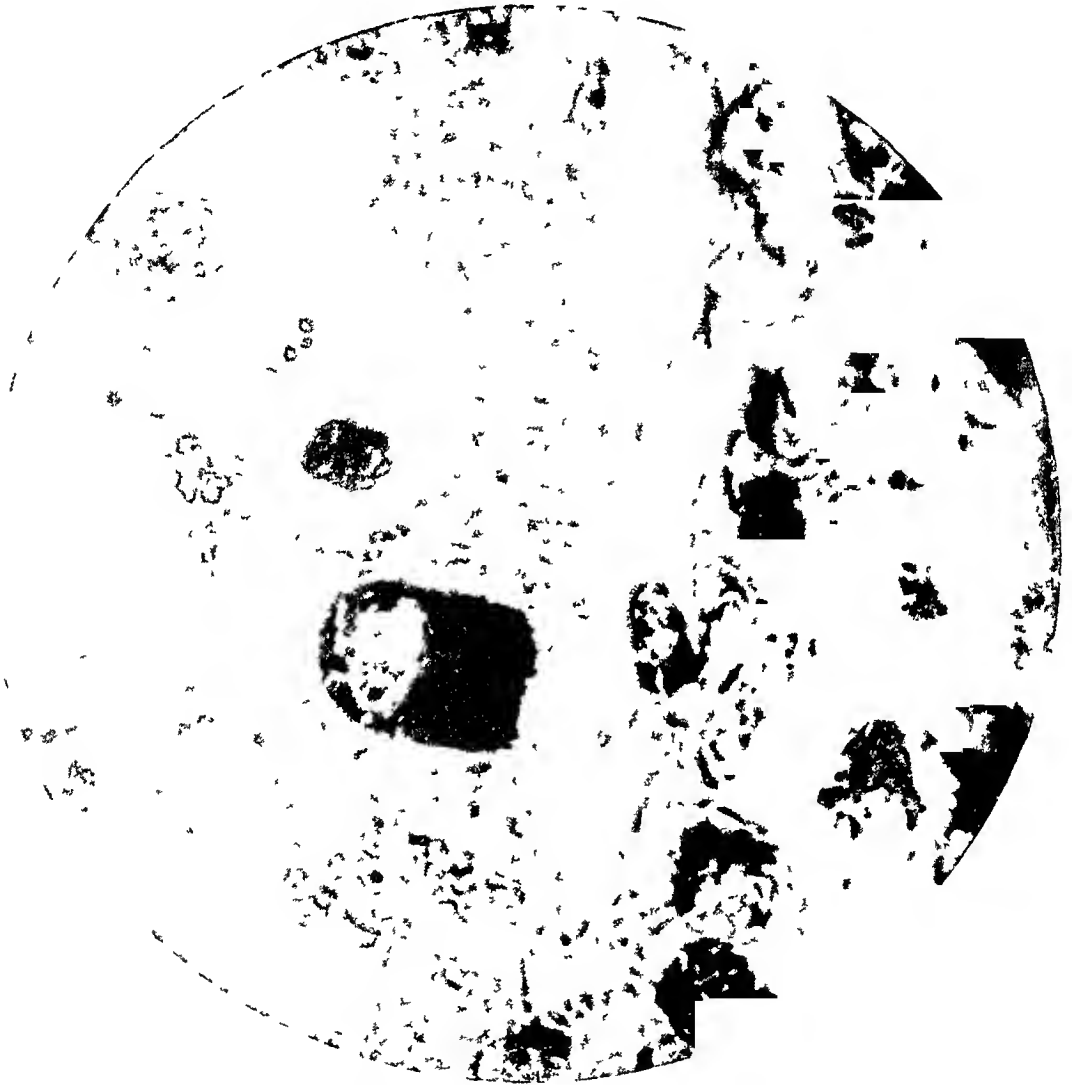


Fig. 6—A high power view of an argentaffin cell the nucleus of which is surrounded by argentaffin granules.

and osmic acid. There are other vacuoles that are stainless, which perhaps is due to the degeneration of the granules, there may also be empty spaces as a result of the extrusion of the granules.

Nucleus—The nucleus is round or oval and appears swollen. It is situated on a higher plane than the nucleus of the cylindrical cell of the glands of Lieberkuhn. It is never in contact with the basement

membrane, but is located almost in the center of the cell. It may be smaller or larger than the nucleus of the cylindric cell, usually they are about equal in size, but the nucleus of the argentaffin cell is somewhat broader. The nucleoplasm is clear and vesicular, and contains a fine sprinkling of chromatin substance that possesses an affinity for silver. In an argentaffin cell that is loaded with granules, the nucleus seems to bubble out from the black granular mass. The nucleus contains a nucleolus and sometimes one or two karyosomes.

PERIGLANDULAR ENTEROCHROMO-ARGENTAFFIN CELLS

Spiafke¹³ stated that the periglandular type of argentaffin cells is found less frequently than the glandular type, however, I have observed that the frequency of both types is about equal. In an examination of 107 appendixes (excluding 4 obliterated appendixes) I found that 43 showed glandular argentaffin cells, 37 periglandular argentaffin cells, 21 both glandular and periglandular cells, 22 the glandular type only, and 16 the periglandular type only.

The periglandular argentaffin cells are usually located near the crypts or embedded in a hypertrophied and hyperplastic periglandular nerve plexus. Very rarely are they seen in contact with the basement layer of the epithelial lining. They are not found in the lymphoid interstices nor beyond Meissner's plexus, but in obliterated appendixes they are seen near the inner muscular coat, singly, in pairs or in groups of from three to twenty-five cells (fig. 1).

Morphologically, the periglandular chromo-argentaffin cells vary considerably. They possess no constant form nor almost constant size, as do the glandular argentaffin cells. The periglandular cells may be pyramidal, spheroidal or polyhedral, they may be smaller or three times larger than the largest glandular argentaffin cells. Usually the periglandular cells are about one and one-half times larger than the glandular type.

Masson classified the periglandular argentaffin cells into four types:

- 1 Neurocrine. This type is made up of polygonal or rounded cells, the cytoplasm of which is very granular and hollowed out by vacuoles containing lipoids.
- 2 Schwannian. The nucleus of the Schwannian cell is enclosed in neuroglial syncytium, the cytoplasm contains few granules.
- 3 Ganglion. The ganglion argentaffin cell has the contour of a ganglion cell, the nucleus is vesicular and contains a nucleolus.
- 4 Intestinal. The cells of this type are arranged in rosets, only the basal portion of the cytoplasm contains granules.

The fourth type could not be demonstrated in the periglandular or subglandular tissues. All of the periglandular argentaffin cells that were observed contained granules, in greater or lesser degrees, throughout the cytoplasm, polar collections of granules in these cells were not seen.

In this paper, it is not urged or even suggested that Masson's classification be modified or revised. Masson's investigations of the argentaffin bodies have been extensive, and his publications regarding them have not yet been equaled. However, as an expression of diligent observation, I must classify the periglandular argentaffin cells as I saw

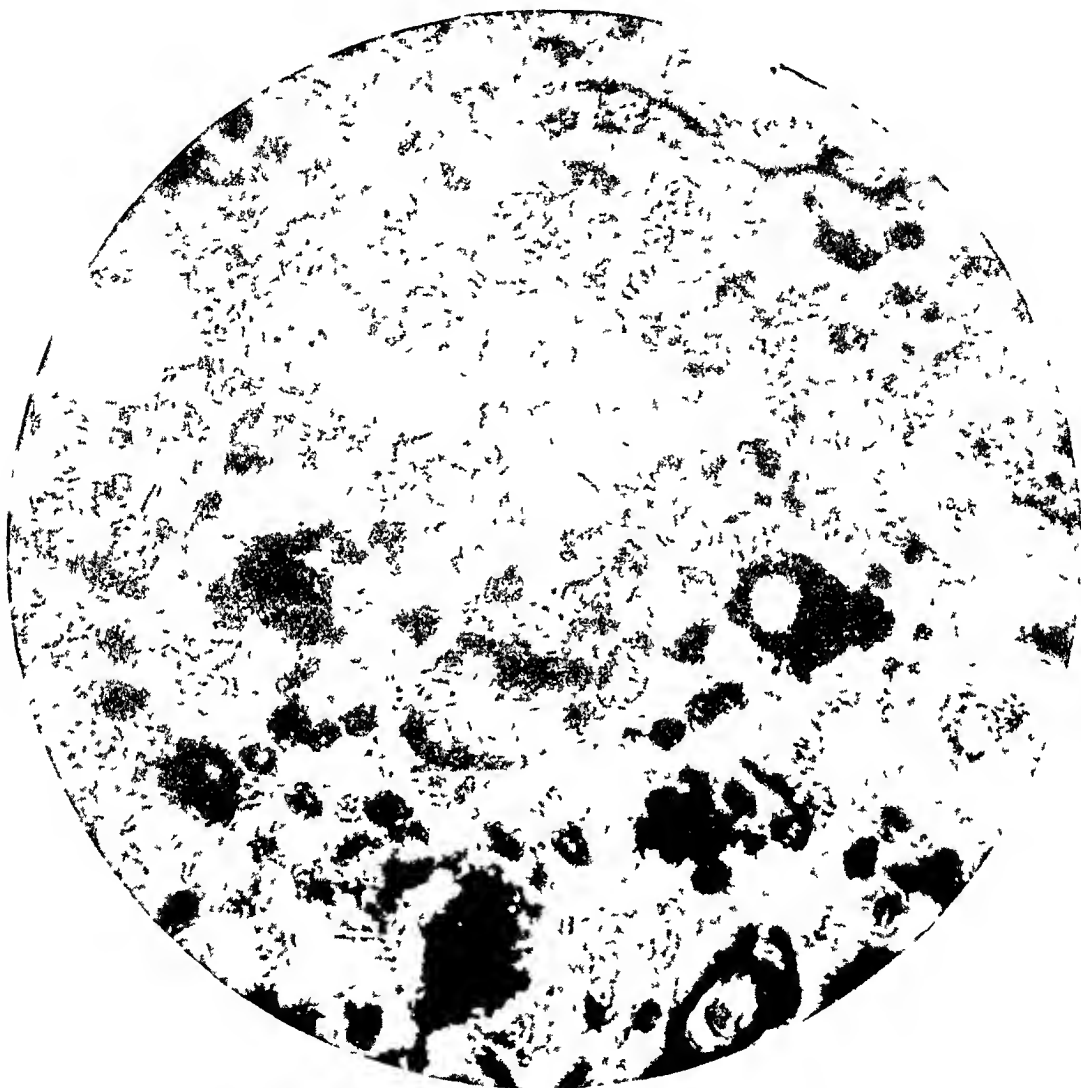


Fig 7 —High power of the epithelial type of the periglandular argentaffin cells

them under the microscope. They may be considered as of the following types: (1) epithelial, (2) syncytial and (3) ganglionic.

Epithelial Type (fig 1) —The epithelial type of the periglandular argentaffin cells is always in close proximity to but not contiguous with the basement membrane of the cylindrical cells that line the gastro-intestinal tract. It is large, spheroidal and sometimes pyramidal. The outline is smooth, with no processes or pseudopods. The cytoplasm contains a

more or less uniform and abundant distribution of various-sized argentaffin granules but occasionally may show a slight concentration in one or two places of the cytoplasm. The entire outline of the nucleus is seldom seen, this is due to the abundance of granules in the cytoplasm. Frequently the nucleus is entirely concealed. Whenever the nucleus is seen, it is found almost centrally located and appears as a lightly stained round or oval body sprinkled with a fine chromatin substance.

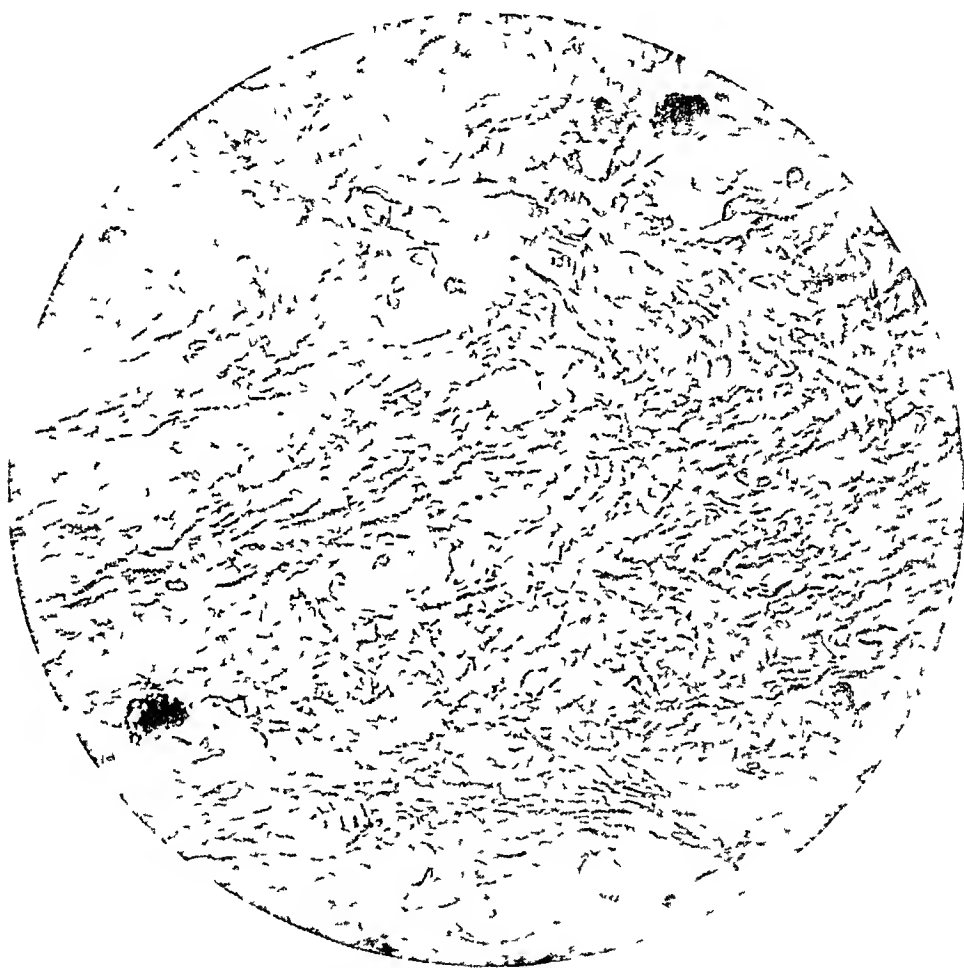


Fig. 8—Obliterated appendix showing eleven periglandular argentaffin cells of the syncytial and ganglionic types

Syncytial Type—This cell possesses no distinct cytoplasmic covering, and can only be recognized as a defined granular area with an almost centrally located, lightly staining nucleus. The granules are variable in size and amount. Sometimes the cell contains only about a dozen granules around the nucleus, but usually the entire cell is densely filled with granules. Frequently the nucleus is seen within a group of neuroglial fibers, and appears to be in close relation with these fibers.

According to Masson, "These argentaffin cells are no longer individualized, they form an integral part of the Schwannian syncytium"

Ganglionic Type (fig 8)—The ganglionic type is moderately granular. The outline of the cell is well evident and shows one or two processes. The nucleus is vesicular, stains lightly and may contain one or two nucleoli.

The last two types are usually seen farther from the crypts and more into the depths of the periglandular plexus. Their most frequent habitat is the axial connective and neuroglial tissues of the obliterated appendixes. Three of the four obliterated appendixes that were examined contained both the syncytial and the ganglionic type.

MIGRATION

Masson efficiently demonstrated and described the migratory tendencies of the argentaffin cells. Migration, according to Masson, is possible by the budding of the tip of the gland of Lieberkuhn. Budding begins with an increase of nuclei at or near the tip of the crypt, and the resulting pseudopod enlarges and appears to contain a multinucleated syncytial mass. As soon as the bud begins to separate from the crypt, the cytoplasm becomes more and more granular. When the bud has broken, the syncytial mass of cytoplasm, nuclei and granules differentiates into the various types of periglandular argentaffin cells.

Sprafke,¹³ Hampeil,¹¹ and Eios¹² and others have not demonstrated such an interesting phenomenon. I was unable to see the least possible suggestion of budding. However, I am inclined to surmise that the epithelial periglandular argentaffin cells originate from the glandular argentaffin cells, but thus far the work done has been insufficient to warrant a substantial account of their presence in the periglandular plexus.

CLINICAL SIGNIFICANCE

Clinically, the significance of the argentaffin cells is perhaps of small importance. The condition known as pseudo-appendicitis may be explained by the "phenomenon of Masson," e. g., the migration of the glandular argentaffin cells into the nerve plexus, causing it to hypertrophy. These hypertrophied and hyperplastic nerve elements, known as neuromas, may produce pain and cause one to suffer from an apparently normal, noninflamed appendix.

Another interesting fact that is worth mentioning is that the entero-chromo-argentaffin cells are the genetic cells of the carcinoids of the gastro-intestinal tract. Masson, Forbus, Sprafke and others have already ascertained the argentaffin origin of the carcinoids. The following is a description of a carcinoid that was recently studied.

The tumor was located 1 cm from the distal end of the appendix. It was 6 mm in diameter, yellowish and firm. The lumen of the appendix in this region was almost entirely obliterated. Microscopically, the carcinoid was seen to occupy the mucosal and submucosal regions. The cells were arranged in nests and strands separated by fibrous septums. Now and then one could see solid masses of cells surrounded by a fibronervous capsule (fig 9). There were occasional areas of homogeneous substance enclosed by epithelial cells. The cells were round or oval and slightly variable in size, those that were located in the center of the nests were round and somewhat smaller than the cells in the periphery. The



Fig 9—Carcinoid of an appendix showing a solid adenomatous growth. There are light spaces bordered by argentaffin cells. The cells reduced silver sluggishly. They stained dark brown with Masson's method.

nuclei were round or oval and vesicular, and contained a moderate amount of chromatin, sometimes nucleoli were seen. The cytoplasm was rather evenly distributed with fine and coarse granules and few vacuoles. The granules reduced silver rather sluggishly and therefore were colored dark brown.

Histologically, there are a few interesting factors that may be mentioned concerning the variability of the argentaffin cells in certain pathologic changes of the appendix.

Spiafke¹³ found that in normal appendixes and in those with mild inflammatory changes, the ratio of negative to positive results in examination for argentaffin cells was 3:1, whereas in marked inflammatory appendixes the ratio was 1:3.

Elios,¹² in almost every instance, was able to demonstrate chromo-argentaffin cells in appendixes the mucosa of which had not undergone severe inflammatory changes. He examined twenty-eight appendixes removed at operation and demonstrated argentaffin cells in all but four. In these, the mucosa was denuded and the submucosa edematous.

The investigations that prompted this paper yielded results as set forth in the accompanying table.

Results of Examination of Appendixes for Enterochromo-Argentaffin Cells, with Relation to Clinical Conditions

	Total	Positive	Negative
Appendixes examined	111	59	52
Appendixes obtained at necropsy	45		
Apparently normal	37	19	18
Obliterated	2	1	1
Chronic fibrous	2	1	1
Atrophic	1		1
Showing acute appendicitis	1	1	
Showing hyperplasia of the lymph follicles	1		1
Showing gross evidence of postmortem changes	1		1
Appendixes obtained at operation	66		
Showing chronic appendicitis	32	21	11
Showing acute appendicitis	20	9	11
Showing subacute appendicitis	8	5	3
Showing gangrenous appendicitis	2		2
Obliterated	2	2	
Normal	2		2

From the results one cannot form definite conclusions. The chronically inflamed appendix demonstrates a predilection of the argentaffin cells for this tissue, the gangrenous and severely inflammatory appendixes are always negative for these cells, the appendixes showing mild and moderately acute inflammatory conditions presented argentaffin cells in 50 per cent of the cases. However, the same is true for the normal appendix.

An attempt was made to associate the presence of the argentaffin cells with the lymphoid character, the glandularity and the nerve distribution, respectively, but since the results were of so fluctuating a nature, a precise statement concerning their relationship cannot be made. It suffices to say that usually when the appendix possessed a scanty periglandular nerve plexus, the argentaffin cells were absent, but when the periglandular argentaffin cells were present, the nerve plexus appeared to be well developed.

Age is a minor factor in the distribution of the chromo-argentaffin cells of the intestinal tract. Masson claimed that the argentaffin character of the appendix lessens with age, the optimum, according to

his investigation, is from fifteen to twenty years. Others contend that the age factor plays a minor rôle in the argentaffin cellularity of the appendix. I found an abundant distribution of argentaffin cells in the appendix of a man 71 years of age whereas on several occasions I was unable to demonstrate them in the appendixes of youths.

The number of positive results in the examination of apparently normal appendixes obtained at necropsy was, in comparison with the numbers reported by other investigators, rather low. Slightly over 50 per cent presented argentaffin cells in the mucosa or submucosa. Perhaps the slight postmortem change destroys the argentaffin granules.

SUMMARY

The literature tracing the development of the chromo-argentaffin cells has been reviewed in chronologic order.

Attention is called to the fact that the Kultschitzky-Schmidt-Ciaccio cells are the same as the chromo-argentaffin cells of Masson.

The glandular argentaffin cells specifically belong to the intestinal tract and may be termed enterochromo-argentaffin cells.

The periglandular argentaffin cells are morphologically so variable and their origin is so uncertain that no definite classification is possible at present.

From the results of this investigation no definite conclusions can be formed concerning the pathologic significance of the argentaffin cells.

EXPERIMENTAL RHEUMATIC LESIONS IN DOGS AND IN RABBITS¹

V H MOON, M D
AND
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PHILADELPHIA

It is not the purpose in this paper to review the subject of rheumatism. Comprehensive discussions of its various phases have recently appeared.¹ The infectious character of rheumatism is generally accepted, as is also the frequent, if not constant, association of streptococci with rheumatic disease. Opinion is divided as to the exact nature of this association. One interpretation is that streptococci are the etiologic agents, of which the lesions of rheumatism are the pathologic effects. Another interpretation is that the primary etiologic agent has not yet been demonstrated, and that the streptococci are merely secondary invaders, the effects of which may be superimposed on or combined with those of the unknown organism. This interpretation is supported by the belief that the lesions of rheumatism are specific and represent the effects of the infectious agent somewhat as the tubercle does in tuberculosis. The difficulty of reproducing rheumatic lesions in characteristic form experimentally has contributed to the uncertainty regarding the etiology of the condition. Such experimental lesions have been reported by many workers.² The evidence presented, however, has not been sufficient to convince every one that the experimental lesions presented the specific features of rheumatism. While conducting experiments on chronic focal infections with streptococci, we obtained results that are of interest because of their bearing on the pathogenesis of rheumatic lesions.

¹ Submitted for publication, July 11, 1930.

² From the Department of Pathology, Jefferson Medical College.

³ This work was made possible by funds from the Martin Research Foundation.

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SOURCE OF MATERIAL

In a case of subacute bacterial endocarditis, a pure culture of a streptococcus of the *viridans* group was obtained from the blood stream during life and from the mitral vegetations at postmortem examination

The patient, a white mechanic, aged 25, had repeated attacks of rheumatism, which began when he was 15 years of age. The first attack lasted four months, the second, two months, the third attack, five years ago, lasted several weeks. He was subject to frequent attacks of sore throat and tonsillitis. The present illness dated from a severe "cold" contracted five months before. Small, red, painful spots appeared in the skin of the fingers and toes. Increasing dyspnea developed on exertion, there were nausea and vomiting, weakness and decreased appetite and a loss of about 28 pounds (12.7 Kg) in weight. The maximum cardiac impulse was in the fourth and fifth interspaces 15 cm to the left of the mid-sternal line. The heart sounds were loud, with a booming first sound, a soft diastolic murmur and a rough systolic murmur transmitted to the axilla. The pulmonic second sound was increased. The liver extended about 4 cm below the costal margin. The spleen was palpable. The temperature curve was irregular, with elevations of from 1 to 4 degrees above normal. Moderate anemia developed, with red cell counts ranging from 3,000,000 to 2,400,000. The leukocyte count ranged from 6,000 to 16,800 per cubic millimeter of blood. There were repeated showers of petechiae. The urine contained a small amount of albumin, in some specimens there were coarsely and finely granular casts. Painful swelling developed in the left hand and wrist. This subsided in a few days. A partial unilateral hemiplegia occurred, from which recovery was gradual. The evidences of illness gradually became more marked. Nine weeks after admission death occurred from cardiac failure. Postmortem examination (Dr B. L. Crawford) showed vegetative mitral endocarditis, vegetative auricular endocarditis, moderate mitral sclerosis, disseminated perivascular fibrosis of the myocardium, serous pericardial effusion, bilateral bronchopneumonia with edema, multiple infarctions of the spleen, kidneys and myocardium and chronic glomerulonephritis.

A fragment of thrombus from a vegetation on the mitral valve was crushed and suspended in salt solution. This suspension was streaked on blood agar plates. After twenty-four hours these plates contained hundreds of minute, firm, dry, discrete colonies, which did not spread readily when rubbed with a wire loop. The colonies were surrounded by a narrow zone of partial hemolysis, and had a distinct greenish color by transmitted light. An isolated single colony was planted into a flask of ascitic broth, which, on the following day, was used for inoculation of the animals. In broth the organisms tended to adhere in small spherical masses. There was no diffuse turbidity of the broth. Only a few chains and pairs of organisms, isolated from the globular masses, were seen in spreads made from the broth culture. This streptococcus grew readily in dextrose hormone broth and in plain broth to which serum, blood or aseptic fluid had been added. It did not liquefy gelatin. When grown in sugar-free broth to which pure sugars were added, it produced acid on dextrose, lactose, saccharose, maltose, levulose, galactose and inulin. Since streptococci of this group rarely ferment inulin, this reaction was questioned and was verified repeatedly. Litmus milk was acidified and coagulated. Mannite was unchanged.

LESIONS IN INOCULATED ANIMALS

Four healthy, vigorous pups about 10 weeks old were each given the sediment from 2 cc of a twenty-four hour ascitic broth culture

intravenously At the same time a focus of infection was made in each by implanting the organism in the peritoneal cavity on a cotton plug by means of a trocar and cannula These animals will be referred to as D 38, D 39, D 40 and D 41 Four young rabbits, weighing from 875 to 1,000 Gm each, were inoculated similarly They will be referred to as R 96, R 97, R 98 and R 99

Within forty-eight hours each of the pups presented swollen, tender joints The joint capsules were distended with serous effusion The arthritis had a definite migratory character In the joints first involved the swelling and tenderness subsided, and a similar condition developed in other joints This arthritis tended to subside in about ten days No purulent arthritis developed In a few joints there was slight residual stiffness The temperature of these animals ranged from 101 to 103.4 F The leukocytic count ranged from 10,000 to 24,000 The hemoglobin and red cell count declined 30 per cent to 40 per cent from normal The pups lost flesh, ate little and grew more slowly than untreated pups of the same litter

Two of them manifested peculiar muscular movements These consisted of frequent spasmodic, jerky, uncoordinated, purposeless movements of the legs and, less noticeably, of the trunk and neck Having never seen chorea in dogs, we have no basis for comparison, but this was suggestive of the choreiform movements seen in rheumatic children This manifestation persisted for about a week and subsided gradually

D 41 was killed and examined fourteen days following inoculation The right elbow and left shoulder joints were distended with a mucoid, slightly turbid fluid The bone-marrow was hyperplastic No other gross lesions were present *Streptococcus viridans* was recovered from the fluid of the joints and from the local implantation in the peritoneal cavity Cultures from urine, bile, blood and peritoneal fluid and from the substance of the bone-marrow, spleen, kidney and liver remained sterile

D 39 was killed and examined twenty-four days following inoculation The joints had returned to normal, showing no visible changes The wall of the entire left ventricle (fig 1) was diffusely thickened, white and opaque The tips of the papillary muscles were slightly scarred and contracted The chordae tendineae were thickened The margins of the mitral leaflets were irregularly thickened and contained grayish, translucent nodules, from 1 mm to 3 mm in diameter Such nodules were also present in the upper portion of the leaflets and irregularly throughout the entire lining of the left auricle These tended to occur in groups of from three to ten, near together The surface of one such group had a thin coating of red, thrombotic material which was firmly adherent to the nodules The surfaces of all the other

nodules were smooth. No ulcerations or soft friable vegetations were present. One cluster of nodules was present near the margin of the tricuspid valve. The myocardium contained a few scattered, gray flecks which were barely visible without magnification. The lungs contained many irregular areas of congestion, which were somewhat firm as if partially consolidated. The kidneys were swollen and rather soft. The cortex was pale and grayish. The urine contained albumin. No visible changes were present in other structures. *Streptococcus viridans* was recovered from the thrombotic nodule in the endocardium.



Fig 1—Heart of D 39, showing widely distributed verrucose endocarditis of the mitral and auricular endocardium and thickening of the mitral valve, of the chordae tendineae and of the papillary muscles. There is slight visible fibrosis of the myocardium.

and from the peritoneal implantation. It was not recovered from the blood, urine, bile, peritoneal fluid or joint fluid nor from the substance of the spleen, liver or kidneys.

D 38 was killed and examined twelve weeks after inoculation. The joints had returned to normal without visible change. The lining of the left ventricle and auricle was diffusely thickened and white. There were scattered pearly white nodules, from 1 to 2 mm in diameter, along the margins of the mitral leaflets. No gross significant changes

were found in other structures. *Streptococcus viridans* was recovered from the peritoneal implantation. Cultures from the blood, bile, urine and peritoneal fluid and from the substance of the spleen, liver and kidneys gave negative results.

D 40 was observed during a period of twenty weeks, in the course of which five intravenous and peritoneal reinoculations with the same strain of *Streptococcus* had been made at intervals of from three to four weeks. There was evident stiffness with limitation of motion in the vertebral joints of the lumbar region and of the hips. This dog was inactive and lay quietly much of the time. Otherwise it appeared normal.

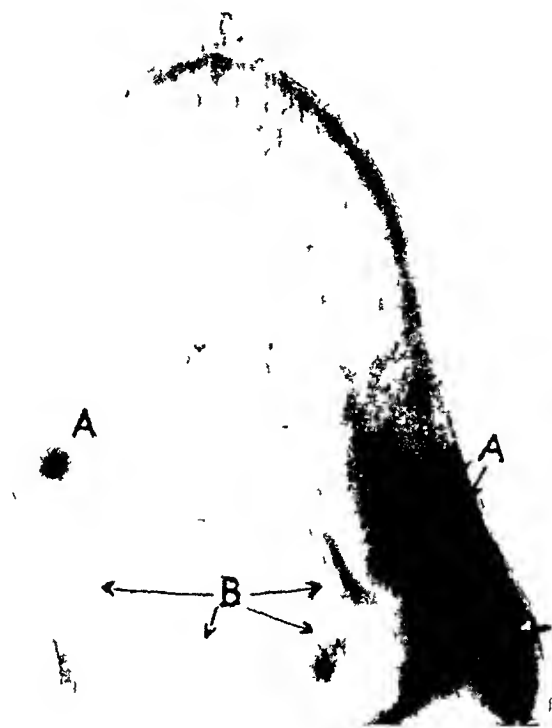


Fig 2—Ear of R 97, showing subcutaneous fibroid nodules at *A*, and small discolored areas at *B*, which are lesions healing without the formation of nodules. This photograph was made by transillumination, the opaque areas are rendered dark.

At postmortem examination the lining of the left auricle and ventricle was diffusely white and moderately thickened. Both the mitral and one of the tricuspid leaflets were scarred and thickened. An area, about 1 cm in each diameter, in the tricuspid valve had a thickness of 2 mm. Along the free margin of the mitral leaflets there was a series of firm, gray, translucent nodules, ranging from 1 mm to 3 mm in diameter. The chordae tendineae were thickened, and the tips of the papillary muscles were slightly scarred and contracted. There was no apparent narrowing of the valvular orifices. The ventricular musculature con-

tained irregular gray flecks and patches, which appeared as scars. There were no gross visible changes in or about the joints. *Streptococcus viridans* was recovered in cultures from the peritoneal implantations only.

Arthritis developed within three days in three of the four rabbits inoculated. The temperature became elevated from 1 to 3 degrees. The leukocyte count ranged from 14,000 to 19,000. The rabbits became ill, ate little and lost flesh rapidly. The loss in weight ranged from 10 per cent to 25 per cent. Numerous red spots, about 2 mm in diameter, appeared in the skin of the ears in three of them. Most of these spots faded after a few days and gradually disappeared. The others persisted, grew somewhat larger and formed firm, fibrous nodules.

TABLE 1—Summary of Features Observed in Rabbits*

Observations	R 96	R 97	R 98	R 99
Days elapsed after inoculation	25	11	4	9
Macroscopic observations				
Effusion into joints	+	+	—	+
Pericardial effusion	+	+	—	—
Subcutaneous nodules	+	+	—	+
Granular mitral vegetations	+	—	+	—
Visible myocardial streaks	+	+	+	—
Visible streaks in skeletal muscle	—	+	+	+
Weight when inoculated, Gm	1,000	1,100	1,050	875
Weight at autopsy, Gm	900	860		675
Microscopic observations				
Submaxillary nodules in myocardium	+	+	+	—
Pulmonary arterial lesions	+	+	—	—

* The signs + and — indicate the presence or absence, respectively, of the items specified.

about 5 mm in diameter (fig 2). *Streptococcus viridans* was recovered in cultures from these nodules during life.

One rabbit, R 99, died nine days following inoculation. The others were killed four days, eleven days and twenty-eight days after inoculation respectively. In three there was mucoid or mucopurulent effusion in the joints. *Streptococcus viridans* was recovered in cultures from the joints of two. Two had firm, granular, thrombotic vegetations on the mitral valve. In two there was marked pericardial effusion. This was serous. No fibrin and no adhesions were present. Cultures from the effusion remained sterile. In three there were firm subcutaneous nodules about the ears. In the heart muscle of three were scattered yellowish or grayish nodules about 1 by 3 mm in size. These were elongated parallel with the muscle fibers and were firm. In three there were similar lesions in the skeletal muscles, involving principally the



Fig 3—Small verrucose or granular vegetations from the auricular lining of D 39 (fig 1) These consist of loose connective tissue containing many vascular channels, $\times 100$



Fig 4—Small granular vegetation from the mitral valve of R 96 A thin coating of firm thrombotic material covered some of these nodules, $\times 100$

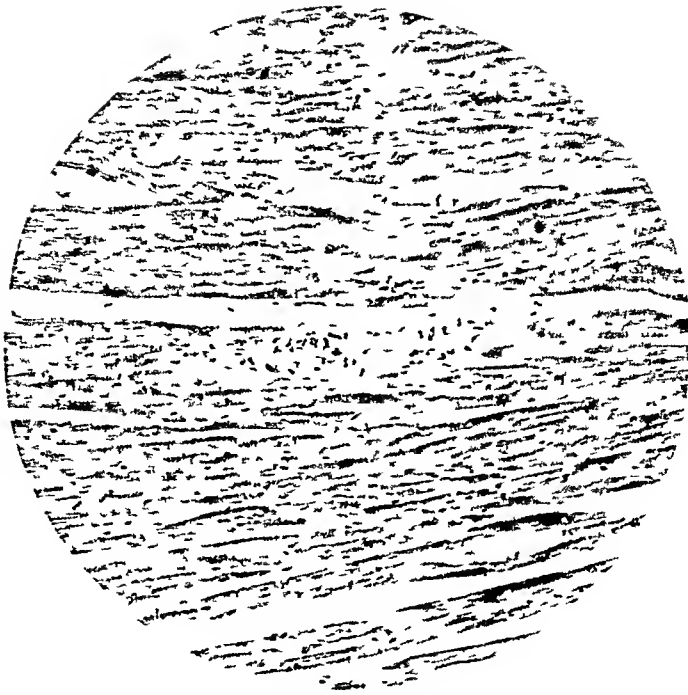


Fig 5—Myocardium of D 39, showing slight edema between the muscle fibers and a localized proliferative inflammatory lesion, $\times 100$

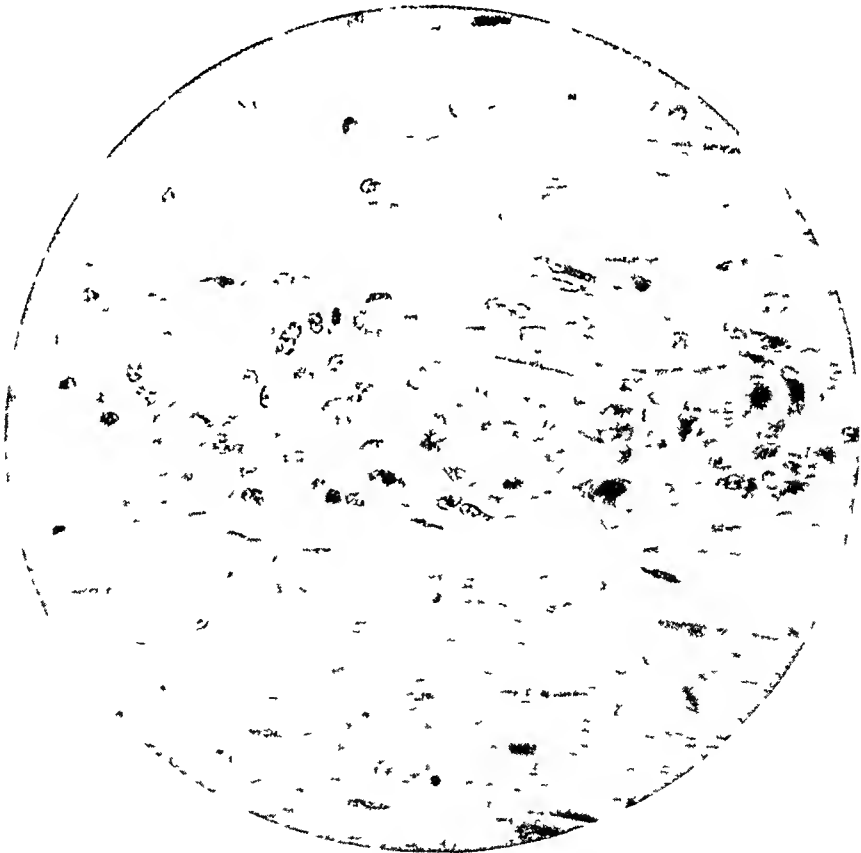


Fig 6—The same lesions as shown in figure 5, $\times 400$ A few necrotic muscle fibers are surrounded by monocytes, some of which have two or three nuclei, plasma cells and fibroblasts

psoas, gluteal and lateral abdominal muscles *Streptococcus viridans* was recovered in cultures from these lesions in the myocardium and skeletal muscles. No visible infarctions were present in any of the organs.

HISTOLOGIC FEATURES OF LESIONS

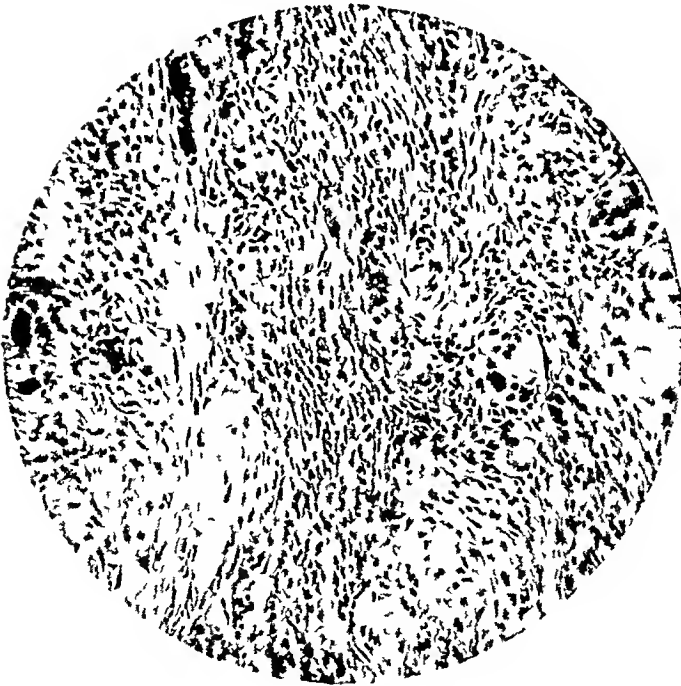
Small, translucent, gray nodules were present along the free margins of the mitral valves of D 39, D 40 and D 41. In D 39 these were present also in the auricular endocardium and on the tricuspid valve. Microscopically, these consisted of rather loosely arranged fibrous tissue and fibroblasts, forming rounded, villous or polypoid projections, covered by intact endothelium (fig 3). These nodules contained small numbers of lymphocytes and monocytes, numerous capillaries and a few larger vascular channels. No thrombotic material was present on or about them. No bacteria could be demonstrated in sections stained by Gram's method. A small bit of firm thrombotic material was adherent to the mitral valve of R 96 (fig 4). In this thrombus and in the nodule beneath it diplococci could be seen plainly in sections stained by Gram's method. Similar nodules were present in the mitral valve of R 98. These lesions were identical in structure with those found along the mitral margins in rheumatic endocarditis occurring in man.

Small localized lesions were found in the myocardium of D 39, R 96, R 97 and R 98. In D 39 these were few and occurred as small accumulations of monocytes, some of which had several nuclei, fibroblasts and lymphocytes, surrounding necrotic muscle fibers. They were not found in any characteristic relationship to arterial structures. In the spaces between muscle fibers throughout the sections there were small accumulations of similar cells (figs 5 and 6).

In R 96, R 97 and R 98 the local lesions in the myocardium were numerous, and in most instances were situated adjacent to or surrounding small arterial branches. In R 98, killed four days after inoculation, the lesions consisted of a number of necrotic muscle fibers surrounded and infiltrated by polymorphonuclear leukocytes, eosinophils and mononuclear cells (fig 7A). In R 97, killed eleven days after inoculation, the larger nodules consisted of remnants of muscle fibers, surrounded by fibrous tissue containing many giant cells, monocytes and a few lymphocytes. The giant cells had homogeneous, slightly basophilic cytoplasm and had from four to twelve pale, oval nuclei. The smaller nodules occurred surrounding or adjacent to arterial twigs. Occasionally the arterial wall itself was involved. The giant cells here were larger. Their cytoplasm extended into the adjoining spaces between cells. There were more numerous fibrous tissue cells and fewer lymphocytes (fig 8A and B). Occasionally calcification was present in these



A



B

Fig 7—*A*, an early stage of a submiliary lesion in the ventricular wall of R 98. A number of necrotic muscle fibers are surrounded and infiltrated by monocytes, lymphocytes and plasma cells. Giant cells are beginning to form. A few leukocytes are present, $\times 200$.

B, a submiliary lesion in the ventricular wall of R 97. This nodule is in a stage more advanced than that in *A*. An arterial branch is present adjacent to this nodule just outside the field to the left. Degenerated muscle fibers are seen at the right and at the left below the center. The black masses are calcified material, $\times 200$.

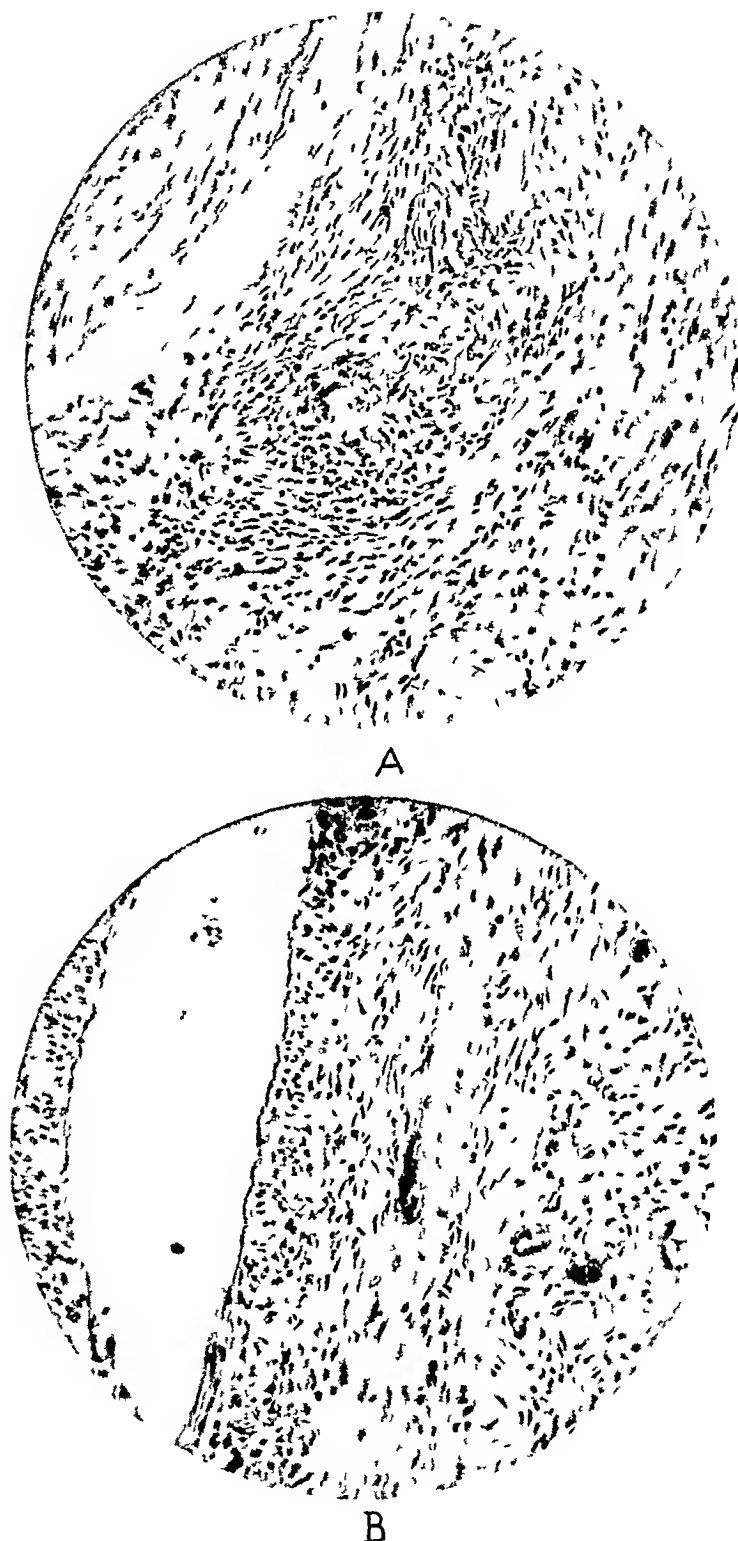
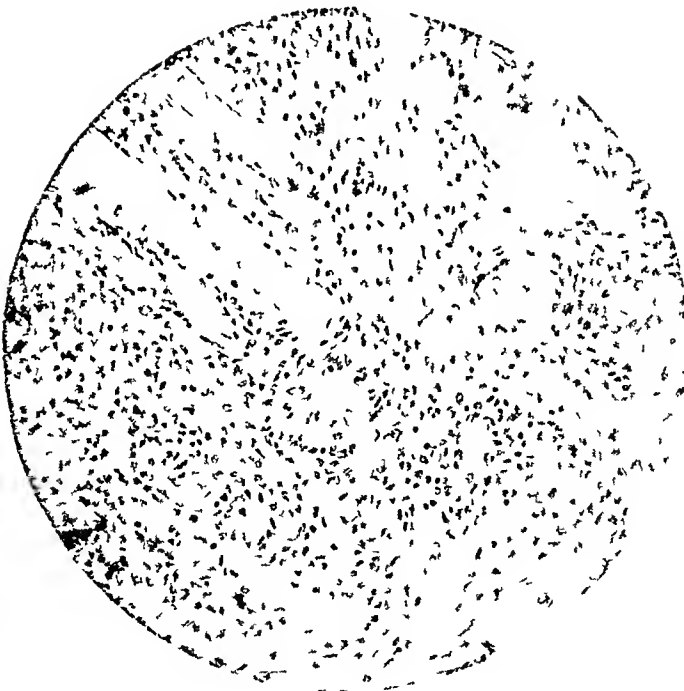


Fig 8—*A*, a smaller lesion than that shown in figure 7*B*. This lesion involves the wall of the adjacent arteriole. Ventricular wall of R 97, $\times 200$. *B*, a small lesion, containing many giant cells, separated from an arterial wall by a few muscle fibers, $\times 200$.



A



B

Fig 9—*A*, a section from the ventricular wall of R 97, stained by Gram's method and magnified 1,000 times. The monocytes and giant cells in a submiliary nodule contain many cocci in pairs, short chains and irregular clumps. Some are seen outside of cells.

B, the margin of a nodular lesion in the psoas muscle of R 99. Necrotic muscle fibers are surrounded by monocytes, small mononuclears and immature fibrous tissue cells. Many giant cells and vascular channels are present, $\times 200$.

lesions The submiliary nodules in the heart muscle of the rabbits were much larger than those in D 39 They varied from 0.1 mm to 1 mm in width and from 0.2 mm to 1.5 mm in length Numerous cocci in pairs and clumps were demonstrable in some of these nodules (fig 9A) In those in which fibrosis was well marked, no bacteria could be seen These nodules presented all the various features that characterize the Aschoff nodule (Clawson³)

The lesions in the skeletal muscles of R 97, R 98 and R 99 were larger than those found in the myocardium and appeared to have no relationship to the arteries Otherwise their structure resembled that of the nodules found in the heart (fig 9B)

The auricular endocardium of D 39 and D 41 was increased to four or five times its normal thickness This increase consisted of fibrous tissue which was distinctly hyaline Beneath it were numerous whorls of fibrous tissue, submiliary in size, which caused the lining to be elevated This gave the auricular endocardium a coarsely granular appearance readily seen in the photograph (fig 1) Grossly these had a yellow color Some of the nodules were markedly calcified In others the deposit of calcium was slight These granules in the endocardium were particularly numerous just above the root of the anterior mitral leaflet and in the auricular appendage Von Glahn⁴ described similar auricular lesions as a prominent feature in rheumatic hearts He found such auricular involvement in nine of thirty-one cases of rheumatic endocarditis He stated that the calcification was superficial, with the altered endocardium lying beneath it In the dog's heart showing this feature, the calcium was deposited in fibrous nodules resembling healed submiliary lesions, lying beneath the thickened endocardium We were unable to demonstrate micro-organisms in sections of the valvular or auricular lesions or in nodules in the myocardium from either of the dogs

The small arteries in both dogs and rabbits and the aorta in one of the dogs, D 38, showed the type of changes which have been described⁵ as occurring in rheumatic disease In the intima and inner portion of the media of the coronary branches in D 39 there was marked proliferation of tissue, resulting in partial obstruction of the lumen There was no apparent proliferation of the endothelium in these vessels In D 38 the vasa vasorum of the aorta were surrounded by small accumulations

3 Clawson (footnote 1, second reference)

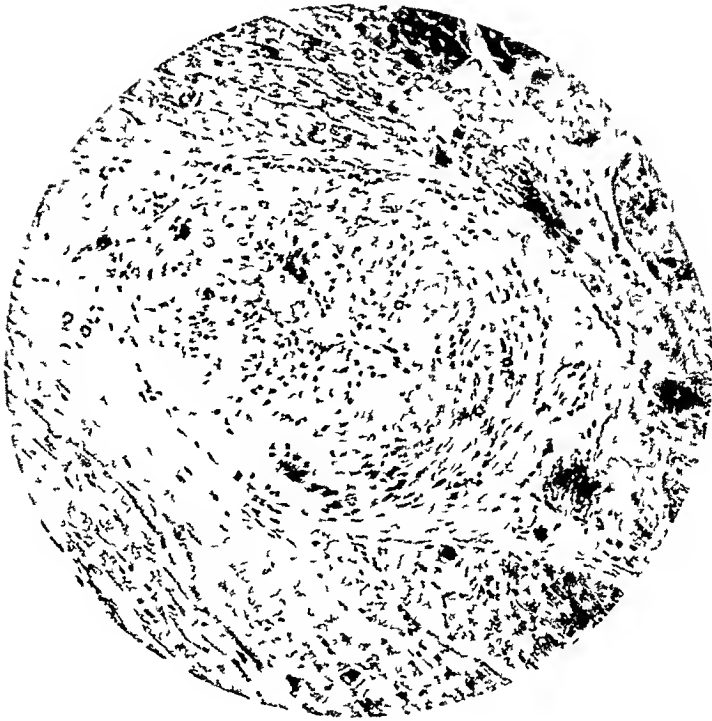
4 Von Glahn, W C Am J Path **2** 1, 1926

5 Klotz, O Tr A Am Physicians **27** 183, 1912 Pappenheimer, A M, and Von Glahn, W C J M Research **44** 489, 1924, Am J Path **2** 235, 1926 Paul, J R Medicine **7** 383, 1928

of monocytes and lymphocytes. In the media there were local accumulations of large monocytes lying between the fibers. Presumably the pressure of the fibers caused the cells to be arranged in thin, flat layers, which in sections appear as rows, as suggested by Pappenheimer and Von Glahn.⁵ There were occasional wedge-shaped fibrous nodules containing large mononuclear cells about the nutrient vessels in the outer margin of the media. In D 40 the vasa vasorum of the ascending aorta were abnormally large and numerous and were conspicuous even in the inner portion of the media. This feature was first described by Klotz.⁵ There were small local areas in the media where the muscular and elastic tissue had disappeared and had been replaced by delicate scars. Nothing resembling Aschoff nodules was seen in this aorta.

The smaller arteries, especially in the lungs, occasionally in the liver, spleen and kidney, showed proliferation of the endothelium, sometimes with narrowing of the lumen, in others, the lumen was completely obstructed. Frequently there were small, irregular vascular channels in the proliferation that filled the lumen. In no case was there evidence of thrombosis. In R 96 and R 99 and in D 38 and D 39 the pulmonary arterioles were markedly involved by proliferation of the endothelium. In R 96 approximately 75 per cent of the arterioles, the diameter of which was not larger than that of a normal renal glomerulus, were involved, as shown in fig 10 *B*. In the alveolar walls were numerous small clumps of densely staining cells with oblong nuclei resembling endothelial cells. We are strongly of the opinion that these represented obliterated capillaries, but since no lumen was demonstrable this could not be verified. A similar change was present in the minute arterioles, the walls of which made identification possible. The alveolar septums adjacent to these clumps were distinctly thickened by fibrous proliferation. In some of the arterioles a definite infiltration of polymorphonuclear and lymphocytic cells was present both within and about the vessel. These were rather numerous in the lung and liver of D 39.

The subcutaneous nodules in the ears of R 99, which was killed nine days after inoculation, each consisted of a necrotic center containing numerous granules from nuclear destruction. Many polymorphonuclear and mononuclear cells were present in and surrounding the necrotic focus. No "palisade arrangement," frequently seen in rheumatic nodules in man, was present. In R 96, killed twenty-eight days after inoculation, these nodules consisted of a ground substance of hyaline material. Surrounding these hyaline areas and between them there was a proliferation of fibrous tissue cells of irregular shape, with no definite arrangement. No leukocytes or mononuclear cells were present. These nodules apparently were well advanced toward healing.



A



B

Fig 10 — *A*, endarteritis with irregular thickening of the wall and narrowing of the lumen Ventricular wall D 39, $\times 200$ *B*, proliferative endarteritis in a branch of the pulmonary artery of R 96, $\times 200$

In the lesions seen in these dogs and rabbits there was no tendency to suppuration even where necrosis was marked. Uniformly the lesions were characterized by the presence of large and small mononuclear cells, giant cells and the formation of fibrous tissue.

LOSS OF VIRULENCE

A culture of the same strain used in the experiments had been kept in laboratory mediums for five weeks. During this time it had been transplanted repeatedly. After twenty-four hours at 37.5 C. the cultures had been held in refrigeration at about 4 C. It was noted that the character of the growth, both in broth and on agar, was modified. The colonies on agar were no longer firm and discrete, but were soft and

TABLE 2—*Summary of Observations in Rabbits Inoculated with Growth of Low Virulence*

Features Noted	R 120	R 130	R 131	R 132
Tenderness of joints	-	+	-	+
Effusion in joints at autopsy	-	-	-	-
Pericardial effusion	-	-	-	-
Subcutaneous nodules	-	-	-	-
Granular mitral vegetations	-	+	-	-
Myocardial streaks	-	-	-	-
Streaks in skeletal muscles	-	-	-	-
Subiliary nodules in myocardium	-	-	-	-
Pulmonary arterial lesions	+	-	-	-

spread readily when touched. In broth the organisms no longer held together in firm masses, but grew in chains, producing turbidity with slight flocculation. The characteristic hemolysis and green discoloration on blood agar remained unchanged. Four young rabbits, weighing about 900 Gm. each, were inoculated in exactly the same manner as the first group described. The joints of two became slightly tender. No swelling was noticeable, and the joints returned to normal within forty-eight hours. The animals lost weight gradually and became anemic. The observations are summarized in table 2.

The organism inoculated was recovered in cultures from the chronic focus in three of these rabbits. In the case of one rabbit, which died some hours before examination was made, postmortem contamination made cultures unsatisfactory. The difference in the manifestations and in the gross and microscopic lesions in these two groups of rabbits was striking. Evidently the pathogenicity of this strain of streptococci was markedly changed by being held for a few weeks in artificial mediums.

SUMMARY

Young dogs and rabbits, not subjected to sensitization or other previous treatment, were inoculated with *Streptococcus viridans* from a case of bacterial endocarditis in man. The manifestations of disease which followed were very similar to the clinical features of acute rheumatic fever.

The gross and microscopic lesions in these animals were identical with those that characterize rheumatic disease. These lesions included verrucose valvular endocarditis, auricular endocarditis with calcification, rheumatic nodules—Aschoff bodies—in the myocardium, lesions of the rheumatic type in the aortic walls, proliferative endarteritis involving small arteries and fibroid nodules in subcutaneous and muscular tissues. Pericarditis with effusion was produced, but no pericardial adhesions.

The organism inoculated was recultivated from some of the lesions and was demonstrated microscopically in sections from others.

These results followed a combination of intravenous inoculation with implantation of chronic focus. It is not maintained that this mode of inoculation was essential to the production of the lesions. We believe the use of young animals and of freshly isolated cultures was of great importance in producing the lesions described.

CONCLUSION

The characteristic lesions of rheumatism can be produced by streptococci. The results obtained strengthen the evidence that streptococci of low virulence are the direct cause of rheumatic disease.

FIBROUS OSTEODYSTROPHY (OSTEITIS FIBROSA) IN EXPERIMENTAL HYPERPARATHYROIDISM OF GUINEA-PIGS*

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In another report,¹ the production of osteitis fibrosa as a result of experimental hyperparathyroidism in dogs was described. Also, the previous experimental attempts to produce this fibrous osteodystrophy and instances of its spontaneous occurrence in dogs, pigs, monkeys, cattle and horses were reviewed.

We decided to study the effects of parathyroid extract (parathormone Collip) on the bones of guinea-pigs, since the guinea-pig had been reported to be "immune" to the action of parathormone. This conclusion was based on the absence of effect on serum calcium following the injection of parathormone. Our experiments on the effects of parathormone on the serum calcium and phosphorus of guinea-pigs failed to corroborate these observations.² With large doses of parathormone we obtained consistent effects on the serum calcium of guinea-pigs, and found that these effects could be brought out more prominently in young animals after prolonged fasting. In addition, changes in the bones were found, particularly in young guinea-pigs, whether hypercalcemia had been found or not.¹ The histologic changes produced in the tissues of the guinea-pigs, especially in the bones, following the injection of parathormone, will be described in detail, and the relation of these changes to nonexperimental osteitis fibrosa of lower animals and man will be indicated. The chemical observations will be touched on briefly. They have been reported elsewhere in greater detail.³

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* From the Laboratory Division, Hospital for Joint Diseases

* Eli Lilly & Company supplied some of the parathormone used in the experiments

1 Jaffe, H. L., and Bodansky, A. J. Exper. Med. **52** 669, 1930

2 Macleod, J. J. R., and Taylor, N. B. Tr. Roy. Soc. Canada (Sect. V Biol. Sc.) **19** 27, 1926. Taylor, N. B. Am. J. Physiol. **76** 221, 1926

3 Bodansky, A., Blair, J. E., and Jaffe, H. L. J. Biol. Chem. **88** 669, 1930

4 Jaffe, H. L., Bodansky, A., and Blair, J. E. Proc. Soc. Exper. Biol. & Med. **27** 710, 1930

THE SPONTANEOUS OCCURRENCE OF OSTEITIS FIBROSA IN RODENTS

Lévy⁵ described an adult tuberculous rabbit in which at autopsy metastatic calcification of the soft tissues was discovered. This led to histologic examination of the bones, which in the gross appeared normal in form and structure. Microscopically, generalized lesions of the bones were discovered, which were most marked in the tibia. There was extensive resorption with enlargement of the canals of blood vessels, resulting in thinning of the cortex. Replacement of the bone by connective tissue was observed in the enlarged canals of the blood vessels and on the surfaces of the cortex, where Howship's lacunae and osteoclasts were present. There was practically no formation of osteoid tissue, and few osteoblasts were observed. The metastatic calcifications were found in the kidneys, lungs, mucosa of the stomach and arterial walls. Lévy did not designate by name the condition that he described, but Christeller,⁶ who restudied material from this case, was inclined to consider it one of acute progressive atrophy of bone, similar to that described by Askanazy in man.⁷ He based his opinion on the fact that osteoblasts and osteoid tissue were practically absent in the greatly fibrosed bone. Because of the rarity of spontaneous fibrous diseases of bone in rabbits, it would be impossible to come to a decision as to whether Lévy's case was one of osteitis fibrosa or one of progressive atrophy of bone, or whether one is a stage of the other. Our experimental results on guinea-pigs indicate that Lévy had a case of true generalized osteitis fibrosa (see comment).

Pick⁸ described a hedgehog, the skeleton of which showed nothing unusual macroscopically. On microscopic examination the bones showed terrific lacunar resorption by osteoclasts, and both the compact and the spongy bone were vascularized, and the enlarged canals of the blood vessels contained connective tissue. Fibrosis of the marrow was also present. The soft tissues showed metastatic calcification. Pick, as others before him, interpreted the metastatic calcification as an indicator of rapid and extensive resorption of bone. He believed that the changes observed in his animal were similar to those described by Askanazy in man and by Lévy in the rabbit, and that his and Lévy's cases represented early stages of osteitis fibrosa, modified in appearance because of differences of the species and somewhat different from the usual cases of osteitis fibrosa in man.

5 Levy, E. *Archiv f. d. Geb. d. Path. u. Bakteriologie* 6 (pt. 2) 555, 1908.

6 Christeller, E. *Ergebn. d. allg. Path.* 20 (pt. 2) 1, 1923.

7 Askanazy, M. *Beiträge zur Knochenpathologie*, Festschr. f. M. Jaffe, Braunschweig, F. Vieweg & Sohn, 1901.

8 Pick, L. *Berl. klin. Wchnschr.* 54 797, 1917.

Pick also agreed with the further point that in lower animals and in man osteitis fibrosa may be diagnosed when there is intensive resorption of bone and fibrosis of the marrow, even without the presence of osteoid tissue. This statement is particularly applicable to lower animals.

THE PARATHYROID GLANDS AND MINERAL METABOLISM

Parathyroid hypersecretion (simple hyperplasia or benign adenoma) has been suggested as the cause of certain clinical dystrophies of bone. It is also known that the injection of parathormone into the dog⁹ and man¹⁰ leads to hypercalcemia and to increased excretion of calcium and phosphorus, particularly in the urine, and to lowered serum phosphorus and hypotonicity. The phenomena of overdosage in the dog have also been described—vomiting, diarrhea, hematuria, hemorrhagic gastroenteritis, impairment of the kidneys, hyperphosphatemia and extensive metastatic calcification in the soft tissues, especially in the kidneys, heart, lungs and gastro-intestinal tract.¹¹

It has also been established that in mice, rats and rabbits, relatively small, if any, effects on serum calcium are produced by the administration of relatively large doses of parathormone. These reports have been reviewed by us in another paper.³

Negative results after massive injections of parathormone in guinea-pigs were reported by Macleod and Taylor and Taylor.² However, we have shown that in guinea-pigs consistent effects on serum calcium and phosphorus could be produced by large doses of parathormone, and that these effects could be brought out more prominently in young animals particularly after prolonged fasting.³ We have also shown that with doses not sufficiently great to produce effects on serum calcium and phosphorus, mobilization and excretion of calcium could be inferred from the microscopic examination of the bones.⁴

It is interesting to note that although Bauer, Aub and Albright¹² injected parathormone into young experimental animals in sufficiently large doses and for sufficiently long periods to suggest the probability that they had produced changes in the bones, they did not study bones histologically. The necessity of subjecting bone to histologic examination has been urged by many pathologists and is emphasized by the cases reported by Levy and Pick. The bones of their animals appeared normal in the gross, but histologically these were greatly diseased.

9 Collip, J. B. *Medicine* **5** 1, 1926. Greenwald, I., and Gross, J. *J. Biol. Chem.* **68** 325, 1926.

10 Hunter, D., and Aub, J. C. *Quart. J. Med.* **20** 123, 1927.

11 Hueper, W. *Metastatic Calcifications in Organs of Dog After Injections of Parathyroid Extract*, *Arch. Path.* **3** 14, 1927. Learner, A. *J. Lab. & Clin. Med.* **14** 921, 1929. Collip (footnote 9).

12 Bauer, W., Aub, J. C., and Albright, F. *J. Exper. Med.* **49** 145, 1929.

METHODS

Nearly all the guinea-pigs used in these experiments were raised in the laboratory. They were kept under hygienic conditions. Their diet consisted of carrots, cabbage, hay and oats. Water was supplied to all animals ad libitum. This diet has been fed to all guinea-pigs in this laboratory, and on it they thrive and reproduce during all seasons of the year.

Some of the experimental animals were caused to fast for long periods (from sixty to seventy-two hours). The experimental animals were given subcutaneous injections of parathyroid extract (parathormone Collip). The serum calcium was determined by the Clark-Collip method and the serum phosphorus by the Benedict-Theis method. Nearly all of the experimental animals were killed to terminate the experiments, and were examined immediately thereafter.

The tissues were fixed either in neutral formaldehyde or Helly's solution. The bones that were fixed in formaldehyde were decalcified in Muller's fluid plus 5 per cent glacial acetic acid, while those fixed in Helly's solution were decalcified in 5 per cent nitric acid. Some of the soft tissues were fixed in 95 per cent alcohol and were stained for calcium by the von Kossa method. The tissues were embedded in paraffin and stained with hematoxylin and eosin.

Four types of experiments were done: (1) on the effects of large single doses of parathormone on young fed guinea-pigs and on young guinea-pigs that had fasted for various periods, (2) on the effects of large single doses of parathormone on adult fed and fasting guinea-pigs, (3) on the effects of repeated doses of parathormone on young guinea-pigs, (4) on the effects of intermittent treatment of young guinea-pigs with large doses of parathormone (with production of osteoid tissue).

In addition, the bones from nineteen untreated young and old, fed and fasting guinea-pigs were studied as controls for the treated guinea-pigs under the conditions of the experiments. Our experience of several years with the bones of guinea-pigs under a variety of experimental conditions served as an additional control in the interpretation of the changes in the bones. Resorption of bone, which is a prominent feature of these lesions, has been discussed by one of us¹³

EFFECTS OF A LARGE SINGLE DOSE OF PARATHORMONE ON THE BONES

In Young Guinea-Pigs Fed to the Time They Were Killed—Eleven guinea-pigs, each weighing between 280 and 368 Gm., were given a subcutaneous injection of 20 units of parathormone per hundred grams of body weight. They were killed at intervals of six, twelve, eighteen, twenty-four, thirty-six and forty-eight hours after the administration of parathormone.

At six hours, examination of the ribs showed slight congestion of the marrow in the vicinity of the costochondral junction, and definite, but slight, subperiosteal resorption, as indicated by the presence of a number of Howship's lacunae and osteoclasts on the shafts of the ribs. At twelve hours after the injection of parathormone, the ribs showed

13 Jaffe, H. L. *Am J Path* 5:323, 1929, Resorption of Bone, Consideration of Underlying Processes, Particularly in Pathologic Conditions, *Arch Surg* 20:355, 1930.

more advanced changes subperiosteal resorption was more advanced, the lacunae containing osteoclasts, the canals of blood vessels of the compacta were enlarged, and the marrow had undergone some fibrous replacement at the costochondral junctions, where the new formation of endochondral bone showed signs of diminution. By the eighteenth hour, the changes had advanced further. Howship's lacunae beneath the periosteum of the shaft were now very deep and contained fibrous tissue and osteoclasts, underneath the endosteum was an attempt at formation of bone, the canals of blood vessels of the shafts of the ribs were enlarged and contained connective tissue, fibrous tissue replacement was observed in the marrow at the costochondral junction and was considerable in one of the animals, new endochondral ossification had ceased at the costochondral junction. Ribs from the guinea-pig killed twenty-four hours after the injection of parathormone showed changes of about the same degree. However, the ribs of an animal examined thirty-six hours after the administration of parathormone showed still more pronounced changes. The resorption of bone was extensive, subperiosteally, the cortex showed considerable excavation, deep Howship's lacunae with osteoclasts on their walls, and connective tissue, there was replacement of the lymphoid marrow by connective tissue, most marked at the costochondral junction, where it filled the marrow cavity and extended for a considerable distance immediately underneath the cortex. By the forty-eighth hour, even more extensive changes were observed. The cortex near the costochondral junctions was fractured, owing to severe decalcification, the rest of the shaft showed extensive resorption, the canals of blood vessels were much enlarged and contained fibrous tissue, there was very extensive hemorrhage and edema of the marrow at the costochondral junction, where the marrow was also fibrosed, formation of bone had ceased, particularly at the costochondral junction.

Young guinea-pigs, therefore, receiving a large single dose of parathormone, showed definite, but slight, histologic changes as early as the sixth hour after the administration of parathormone, which became progressively more intense to the forty-eighth hour, the longest interval of time employed. At this period decalcification was so marked that the cortices of the ribs were frequently fractured. Often the cortex near the costochondral junction was converted into a pink-staining tissue consisting of disorganized fibrils of bone, and the fibrils remained after removal of the inorganic constituents of the matrix. These results were striking evidence of the severe and extensive decalcification that one large dose of parathormone is capable of inducing in guinea-pigs. See figure 1.

Study of the serum calcium and phosphorus of these eleven animals showed a slight variation from the normal. The calcium tended to be

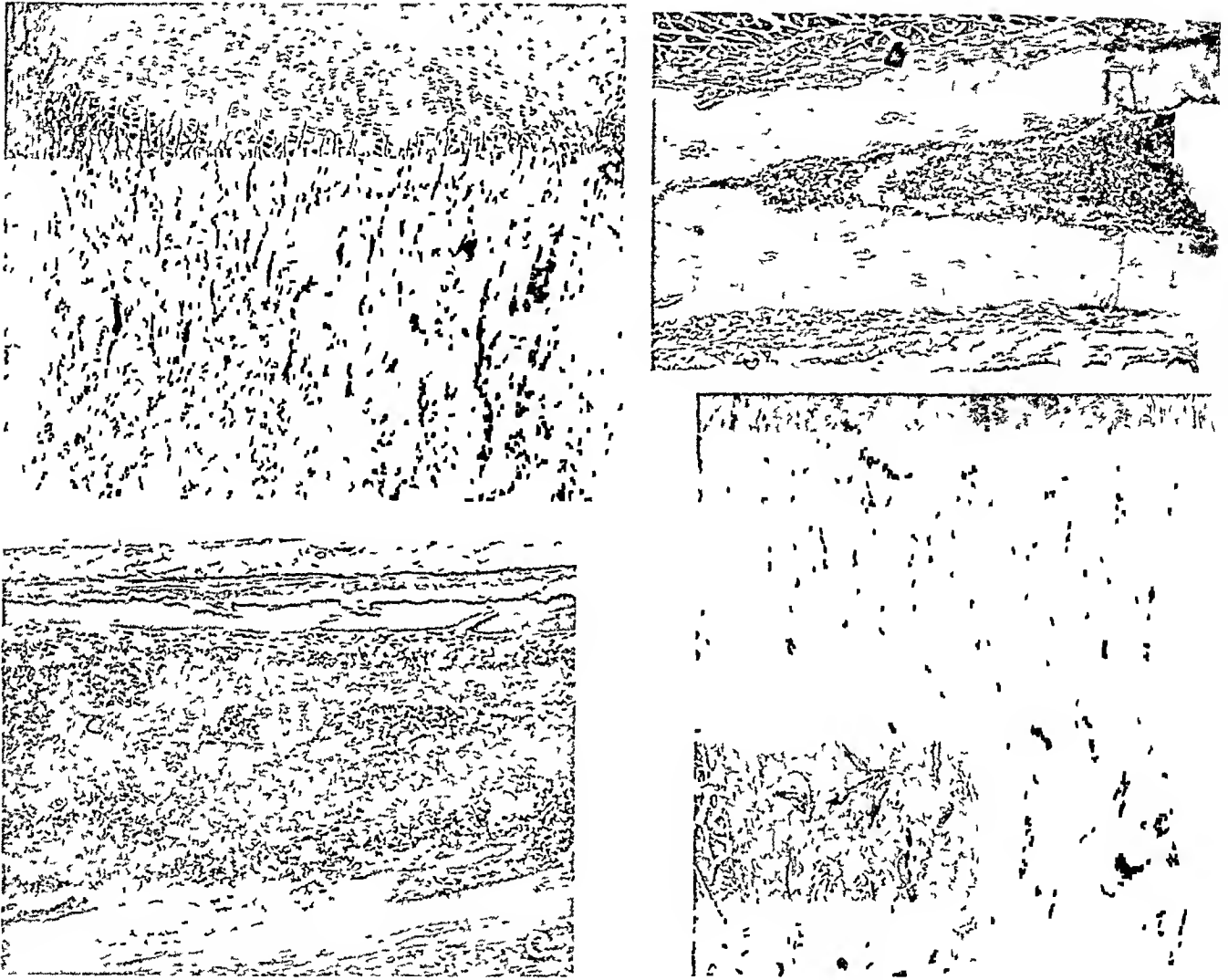


Fig 1—*A*, the costochondral junction of a rib of a young control guinea-pig weighting 280 Gm. The cartilage columns are regular, and endochondral ossification is active, the lymphoid marrow extends to the costochondral junction. Magnification, $\times 60$. *B*, the shaft of the rib shown in *A*. The cortex is compact, the canals of the blood vessels are small, lymphoid marrow occupies the medullary cavity. Magnification, $\times 60$. *C*, the shaft of the rib of a young guinea-pig weighing 300 Gm. The animal was killed forty-eight hours after the injection of 60 units of parathormone, and had been permitted to feed. The lymphoid marrow has disappeared, and the marrow cavity is filled with blood, the result of free hemorrhage. The cortex already shows extensive resorption and enlargement of the canals of blood vessels. These canals contain fibrous tissue. Magnification, $\times 65$. *D*, the costochondral junction of the rib shown in *C*. The marrow is degenerated, the cortex is fractured in numerous places, the columns of endochondral bone are splintered, and new endochondral ossification has ceased. Magnification, $\times 65$.

higher at twenty-four and thirty-six hours after injection. The serum phosphorus values showed a distribution not far above the zone of the values found for the fed controls.

The striking feature brought out in the study of these eleven guinea-pigs is that in spite of the progressively increasing intensity of the lesions of the bones over a period of forty-eight hours, there was relatively little change in the serum calcium and less in the serum phosphorus. It illustrates the difficulty of obtaining hypercalcemia in young guinea-pigs that are being fed. It shows that nevertheless there was a progressive effect of the parathormone either directly or indirectly, on the bone and bone marrow, and that hyperparathyroidism existed. The results indicate that hypercalcemia should not be used as a sole criterion of hyperparathyroidism. The reasons for the absence of marked hypercalcemia may possibly be found, as we have indicated elsewhere, in an increased rate of the excretion of calcium, or possibly the hypercalcemia was counteracted by feeding, since the diet of our guinea-pigs yields in the course of metabolism a basic balance. It is known that parathyroid hypercalcemia may be decreased by bases.¹⁴

In Young Fasting Guinea-Pigs—Six young guinea-pigs varying in weight from 310 to 360 Gm. were made to fast from sixty to seventy-two hours. At intervals of from three to forty-eight hours before the termination of the experiment, an injection of parathormone was given equivalent to 20 units per hundred grams of body weight. These animals also showed a progression of the pathologic changes, as observed in the ribs of the fed series, becoming more intense to the forty-eighth hour, which was the longest interval of time employed. At this period, decalcification was so marked that the cortex of the ribs was fractured. The cortex near the costochondral junction was converted into a pink-staining tissue, consisting of disorganized fibrils of bone, the fibrils remaining after removal of the organic constituents of the matrix. The changes after forty-eight hours were possibly slightly more severe in the fasting than in the fed animals, although an insufficient number of animals was studied to allow definite conclusions. It is observed, therefore, that changes in the bones after a single large dose of parathormone were of the same order and extent in fed and fasting animals.

The effects of prolonged fasting were, however, reflected in the figures for serum calcium and phosphorus. The results for these six animals, with those for seventeen additional animals the bones of which were not studied microscopically, showed an increase in the serum calcium as early as four hours after the injection, rising to a maximum after from eighteen to thirty-six hours and persisting at a high level to forty-eight hours after the injection. The serum phosphorus in these

14 Stewart, C. P., and Percival, G. H. *Biochem. J.* **21**: 301, 1927.

animals rose high above that of the fasting controls (not receiving parathormone), indicating overdosage

Thus it is observed that prolonged fasting helped to demonstrate hypercalcemia, but the bone changes resulting from the hyperparathyroidism were observed in both fasting and fed animals, with and without hypercalcemia, respectively

That prolonged fasting, as such, could not raise the serum calcium of the guinea-pig or induce the bone changes described was shown by an examination of six fasting young controls, the values of the serum calcium and phosphorus of which were normal, the bones of four of these animals showed, on histologic examination, only the usual effects of starvation on the bone marrow—that is, the opening of innumerable blood sinuses in the marrow. In addition there was diminution in the formation of new endochondral bone at the costochondral junctions. In none of the sections was there much enlargement of the canals of blood vessels, nor was there fibrous invasion of the marrow and bone. An abnormal number of osteoclasts and Howship's lacunae were not observed.

In Adult Guinea-Pigs Fed to the Time They Were Killed—Six adult guinea-pigs, each weighing between 620 and 730 Gm., were given an injection of a single large dose of parathormone (20 units per hundred grams of body weight) twelve, twenty-four and forty-eight hours before they were killed. In no instance were marked effects observed in the bones, such as enlargement of the canals of blood vessels, subperiosteal and subendosteal resorption with osteoclasts in Howship's lacunae, or necrosis of marrow and fibrosis of bone and marrow. The serum calcium tended to rise and was definitely high at twenty-four hours. The serum phosphorus values were slightly above the normal range.

It is almost inconceivable that the large doses of parathormone injected into these adult guinea-pigs did not have some effect on their acid-base equilibrium, with some effects on the calcium reserves of the bone. We have found histologic examination useful in demonstrating the effects of parathormone in the bones of young guinea-pigs, in which we have been able to study the results of experimental hyperparathyroidism. We have observed identical changes in the bones of young guinea-pigs, dogs and rabbits given each a single large dose of parathormone. It is possible that in the adult guinea-pigs, while the histologic examination showed no obvious effects of experimental hyperparathyroidism, chemical analyses, which are capable of greater precision, would have shown slight quantitative differences in the treated adult, as compared with the control adult animals.

We doubt whether these adult guinea-pigs are immune to such large doses of parathormone. They showed definite effects on the serum calcium, and the serum phosphorus also seemed to be affected. We believe, however, that the effects of hyperparathyroidism on the bones may be qualitatively different in young and adult guinea-pigs. Much larger doses of parathormone might have induced severe changes in the bones of the adults. An important qualification in all discussions of the changes in the bones in experimental hyperparathyroidism is that they are most marked in the young animals, in the most actively growing portions of the bone, that is, at the costochondral junctions or in the subepiphyseal regions of the metaphysis or in the ends of the diaphyseal cortex. Clinical cases of osteitis fibrosa cystica, with parathyroid adenoma, likewise occur in young persons, in whom the lesions probably have been developing from infancy or childhood¹⁵. It seems that the physiologic state of the bone is important in eliciting the effects of hyperparathyroidism.

In Adult Fasting Guinea-Pigs—Seven adult guinea-pigs, each weighing between 620 and 860 Gm, were studied. They were made to fast for seventy-two hours before they were killed, and were given an injection of a single large dose of parathormone (20 units per hundred grams of body weight) six, twelve, twenty-four and forty-eight hours before being killed. The bones of none of these animals showed resorption of bone or fibrosis of marrow, though two of them showed a slight increase in the number of subperiosteal and subendosteal osteoclasts, which may in itself have been due to fasting rather than to the parathormone. In these animals the effects on the serum calcium were slight and not much greater than in the fed guinea-pigs. The values of the serum phosphorus were generally slightly above the normal range.

In these doses, therefore, the hyperparathyroidism that was induced was associated with only slight elevation of the serum calcium and phosphorus, and there were no obvious effects on the bones on histologic examination.

EFFECTS OF REPEATED DOSES OF PARATHORMONE ON THE BONES

In Young Growing Guinea-Pigs—As stated in our report of the chemical results,³ the animals used in these experiments were all young, the initial weight of most of them was between 300 and 400 Gm, a few weighed more, 470 Gm being the weight of the heaviest. In order to observe the condition of the guinea-pigs during the progress of the experiments, they were weighed at frequent intervals. Five groups of experiments were carried out. Group 1 included five animals given daily injections of 10 and 20 units for ten and sixteen days. Group 2 included

¹⁵ Hirsch, I. S. *Radiology* **12** 505, 1929, **13** 44, 1929.

two animals treated for thirty-four days, the maximum daily dose was 16 units, preceded in one of the guinea-pigs by previous treatment with smaller doses. Group 3 included animals given preliminary daily treatment with small doses, followed by large doses—up to 60 units. Group 4 consisted of animals receiving large daily doses for three days without preliminary treatment. Group 5 included animals receiving very large daily doses (from 60 to 100 units) for four days after preliminary treatment with smaller doses.

When receiving 10 units or less daily, the animal gained weight. On about 20 units in the short experiments, the weight generally rose. In our longest period thirty-four days, with a daily dose of 16 units, the animals continued to gain until the twenty-third day, then lost relatively rapidly until the twenty-seventh day, after which their weights remained practically stationary. On larger doses, loss of appetite was indicated by stationary or slightly decreased weight, and when the large doses were continued, larger losses in weight occurred.

We noted the effects of the repeated doses of parathormone on the serum calcium and phosphorus. The guinea-pigs were bled usually at the end of the test, but in several cases also during the progress of the test, preferably just before a dose was increased. In view of our observations of the long persistence in guinea-pigs of the effect of a single injection of parathormone, the serum calcium and phosphorus at any time during the course of daily injections were assumed to be under the influence of the last two, or perhaps three, doses injected. The significance of the interval between the last injection and bleeding was therefore reduced.

Our guinea-pigs were bled less than twenty-four hours after removal of food, for we found that after a single injection of parathormone there were no marked differences between the values of the serum calcium and phosphorus of guinea-pigs fed to the time of bleeding and those of guinea-pigs that had fasted for twenty-four hours or less.

Group 1 10 and 20 Units Daily for Ten and Sixteen Days—One animal receiving 10 units of parathormone daily for ten days showed in the sections of the ribs slight subperiosteal resorption with some Howship's lacunae, there was very slight fibrosis of the marrow at the costochondral junction. Three guinea-pigs receiving 10 units daily for sixteen days showed to a great degree similar changes, the lighter animals showing the more severe lesions, because of the relatively larger dose. Sections of their ribs showed a generalized thinning of the cortex. Subperiosteally there was osteoclastic resorption, with Howship's lacunae. Some of the haversian canals of the cortex were enlarged and contained fibrous tissue. There were Howship's lacunae and osteoclasts on the walls. A few perforating canals were observed extending through the entire thickness of the cortex. The marrow was congested, the blood

sinuses were dilated, and a slight amount of free blood was present, with evidence of phagocytosis. The marrow was scarred, especially near the costochondral junction. In this area there was cessation of the formation of new bone, with evidence of osteoclastic resorption. In some of the ribs there was subperiosteal formation of callus. See figure 2.

One animal receiving 20 units daily for ten days showed essentially the same changes.

With these doses of parathormone, no clear effect on the serum calcium was obtained, the average value being within the normal range.

Group 2 Daily Treatment for Thirty-Four Days—One of two animals received 2 units of parathormone daily for eight days, 8 units for seventeen days and 16 units daily for nine days. It showed definite



Fig 2—The shaft of a rib of a guinea-pig weighing 260 Gm when injection with 10 units of parathormone daily was begun. The animal was killed after sixteen days, at this time it weighed 323 Gm. The cortex is thin, there is marked subperiosteal resorption, the canals of blood vessels are enlarged and filled with vascular fibrous tissue, the marrow is congested, and some free hemorrhage is present. Magnification, $\times 65$.

osteoclastic resorption of the cortex of the ribs and femur. The enlarged canals of blood vessels contained fibrous tissue, with some fibrosis of the marrow at the costochondral junction and at the metaphysis. The lesions were somewhat less severe than those observed in guinea-pigs receiving 20 units daily for ten days, the severity of the lesions having probably been modified by the previous preparation with the smaller doses and the greater weight of the animal. The serum calcium on the twenty-fourth day was normal (after seventeen days on 8 units), but on the thirty-fourth day, after nine days on 16 units daily, it was 16.7 mg per hundred cubic centimeters. The serum phosphorus value at this time was apparently normal.

In the other animal, given 16 units daily for the entire thirty-four days, the ribs showed resorption. The canals of blood vessels were enlarged and contained fibrous connective tissue. The marrow at the costochondral junctions and at the metaphyses was fibrosed. The serum calcium was 12.1 mg per hundred cubic centimeters after eight days, and 11.6 mg, on the thirty-fourth day. The serum phosphorus value was normal.

Group 3 Preliminary Daily Treatment With Small Doses, Followed by Large Doses, up to 60 Units on the Last Day—Four guinea-pigs were given 5 units of parathormone daily for two days, 10 units for four days, 20 units for four days, 30 units for four days, 40 units for one day and 60 units for one day. Sections of the ribs and long bones showed pronounced resorption of cortical bone with marked enlargement of the canals of blood vessels, and the canals contained much connective tissue and osteoclasts. The marrow at the costochondral junctions and underneath the epiphyseal cartilage plates was scarred and contained numerous dilated blood sinuses, considerable free hemorrhage and osteoclasts. Formation of endochondral new bone at the epiphyseal cartilage plates and the costochondral junctions had ceased. The changes varied somewhat in degree with the individual animal, one of them showing more acute changes, with acute degeneration of the marrow. See figure 3.

Guinea-pigs showing a greater degree of reaction to the hyperparathyroidism presented edema of the subcutaneous tissues of the abdomen and wall of the chest. These edematous tissues contained numerous eosinophils and many neutrophil leukocytes. The fibers of the heart muscle were degenerated and fragmented in some and showed metastatic calcification. The spleen showed fibrosis. These four guinea-pigs were suffering from acute hyperparathyroidism, the results of which were reflected in both bones and soft tissues. The serum calcium was elevated above normal. The serum phosphorus values were within the normal range.

Group 4 Three Large Daily Doses Without Preliminary Treatment—Three guinea-pigs, each weighing about 320 Gm, were given injections of 20, 40 and 60 units daily on three successive days. They all died during the third day, before the serum calcium could be determined. Their bones and soft tissues showed very severe effects. The ribs were extensively resorbed, the haversian canals being enlarged and containing much fibrous tissue and numerous osteoclasts. At the costochondral junctions there was extensive necrosis of the bone, with very rapid decalcification, resulting in pink-staining areas—masses of disorganized fibrils of bone, the remains of the organic matrix. There was some edema between the fibrils, and the tissue of the disorganized

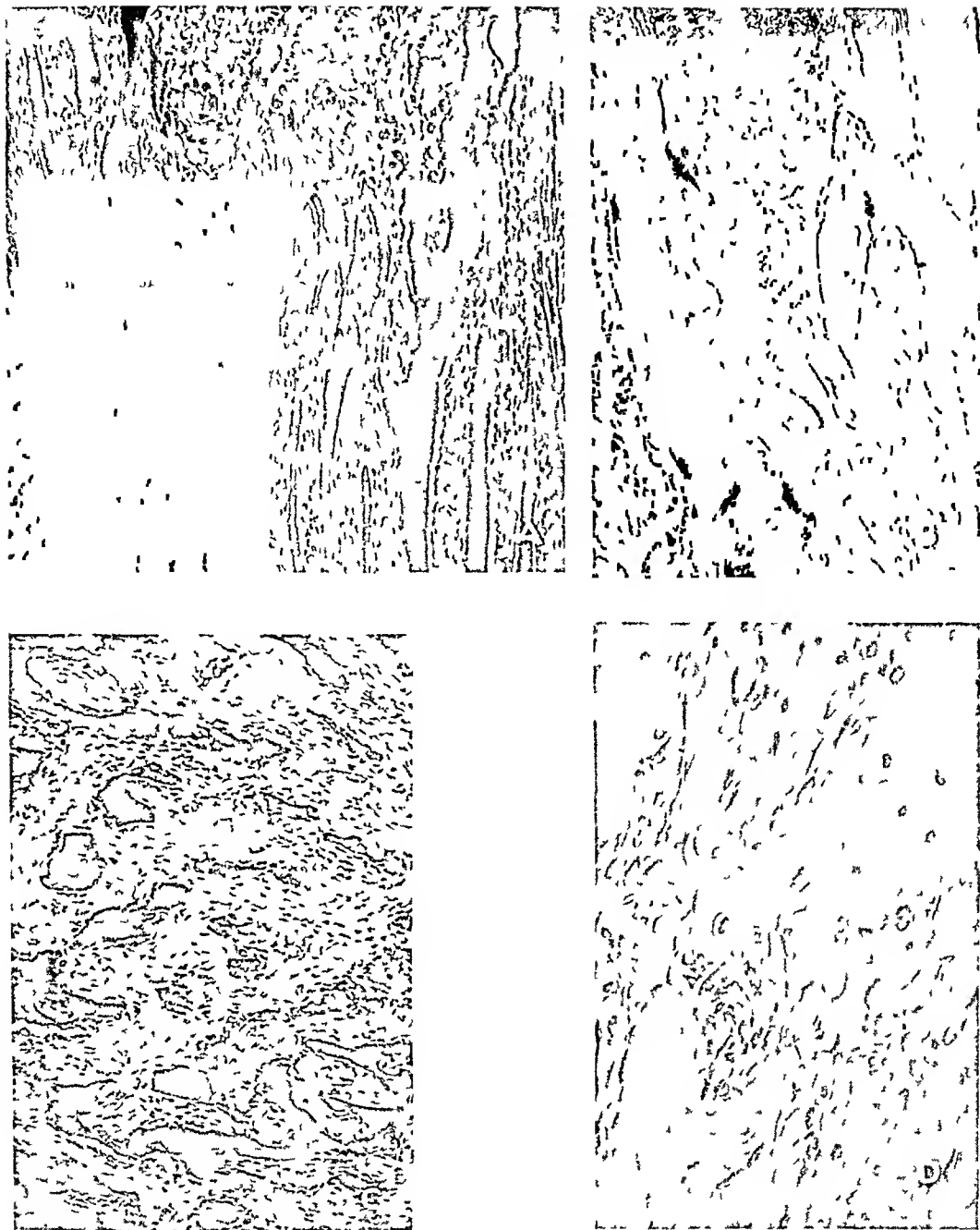


Fig 3—*A*, a section from near the costochondral junction of a rib of a guinea-pig weighing 276 Gm. The guinea-pig was given daily treatment with small doses followed by large doses, up to 60 units on the last day. It was killed sixteen days after the beginning of the experiment, at this time it weighed 356 Gm. The marrow is considerably scarred and contains numerous dilated blood sinuses and osteoclasts. The resorption of bone is pronounced, and the enlarged canals of blood vessels contain much fibrous tissue and osteoclasts in Howship's lacunae. Magnification, $\times 60$. *B*, the shaft of the rib shown in *A*. Marked enlargement of the canals of blood vessels and numerous Howship's lacunae and osteoclasts are observed. Magnification, $\times 60$. *C*, an area of meta-physeal fibrosis in a guinea-pig weighing 270 Gm at the beginning of the experiment and treated like the animal from which *A* and *B* were taken. The guinea-pig weighed 315 Gm when killed. Observe the marked fibrosis of the marrow and resorption of bone. Magnification, $\times 60$. *D*, the details of the osteoclastic resorption of bone and of the fibrosis of the marrow shown in *C*. Magnification, $\times 360$.

matrix had been rapidly vascularized. Formation of new bone had ceased at the costochondral junction, and the trabeculae of bone deposited on the cartilage cores had been dissolved. Throughout the marrow there were areas of necrosis. The necrotic marrow contained numerous neutrophil leukocytes. At the costochondral junction, the marrow was extremely vascularized, somewhat fibrosed and showed free hemorrhage. Fracture of some of the ribs occurred in this region. The changes in the long tubular bones were of the same order as those described in the ribs, and the severest changes in the marrow were found in the metaphyses. Where fractures had occurred in the bones, an attempt at repair by subperiosteal callus was already evident. See figure 4 *A, B* and *C*. The soft tissues in the kidneys, gastric mucosa, lungs and heart showed considerable metastatic calcification. The fibers of the heart muscle were degenerated and fragmented (figure 4 *D*). The subcutaneous tissues of the abdomen showed edema, necrosis and metastatic calcification. Some of the other organs and tissues were congested.

Two guinea-pigs, each weighing about 375 Gm., received 80 units daily for three days, and two received 40 units daily for three days. All died before the blood could be examined. The changes in the bones were as described in the preceding paragraph, but more severe, the necrosis of the marrow being more marked, with large cystic spaces appearing in the marrow at the costochondral junctions and in the metaphysis. See figure 5.

Group 5 Four Very Large Daily Doses (from 60 to 100 Units) after Preliminary Treatment with Smaller Doses—This group showed many striking differences when compared with group 4. After from one to three weeks of preliminary treatment with small doses of parathormone (from 8 to 10 units), the doses were rapidly raised to 60 and even to 100 units daily and maintained at these high points for several days, without the guinea-pigs succumbing. By the end of the experiment, one such animal had been receiving 60 units a day for three days, another, 60 units for four days, and a third, 100 units for four days. The serum calcium was very high in these animals, being 16.9, 20 and 18.5 mg. per hundred cubic centimeters, respectively, at the termination of the experiment, but it is striking that no hyperphosphatemia developed, the serum phosphorus being 7.7, 6.6 and 6.9 mg. per hundred cubic centimeters.

The histologic examination of the bones confirmed the protective effect that is exercised by preliminary treatment with small doses of parathormone. The bones were resorbed, and the enlarged canals of blood vessels contained fibrous tissue, embedded in which were numerous eosinophils. The connective tissue contained numerous osteoclasts.

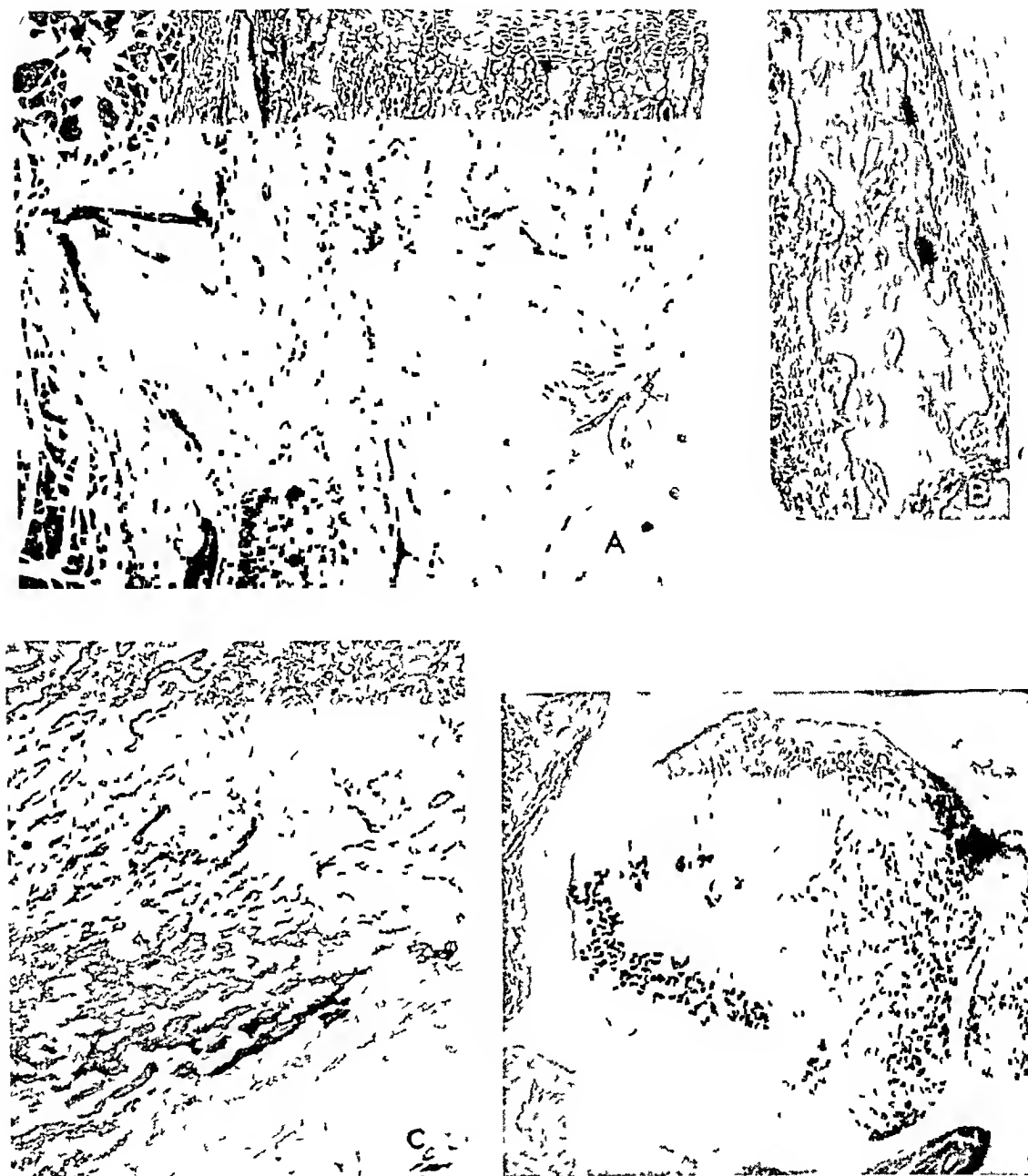


Fig 4—*A*, the costochondral junction of a rib of a guinea-pig weighing 300 Gm, given 20, 40 and 60 units of parathormone on three successive days. There is extensive necrosis of bone and rapid decalcification, fractures are present. Hemorrhage of the marrow and fibrosis are observed. An attempt at subperiosteal repair is present. Magnification, $\times 60$. *B*, cortical resorption of the shaft of a long tubular bone from the same animal as *A*. Magnification, $\times 60$. *C*, shaft of a long tubular bone of a guinea-pig receiving three large doses of parathormone. Note the extensive resorption and fibrosis of the cortex. Magnification, $\times 20$. *D*, the heart muscle of an animal given several large doses of parathormone, metastatic calcification is observed. Von Kossa stain is used. Magnification, $\times 60$.

and the bone showed numerous Howship's lacunae. The marrow was fibrosed, especially at the costochondral junctions and in the metaphyses. The striking feature was the absence of acute degeneration of the marrow, which had been observed in all guinea-pigs given large doses without preliminary treatment.

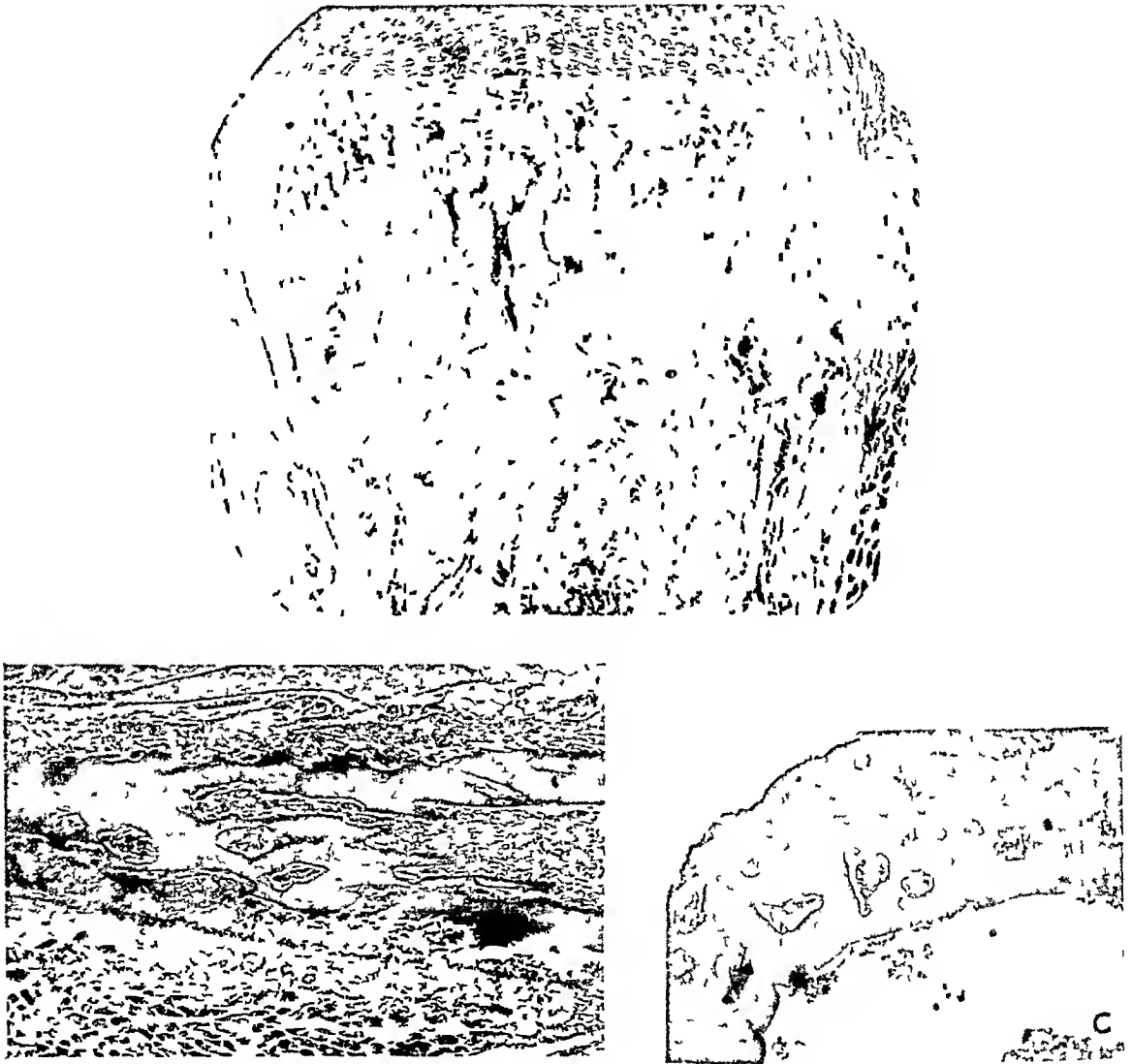


Fig 5—*A*, the costochondral junction of a rib of a guinea-pig weighing 375 Gm, the animal had received 80 units of parathormone for three days. Acute decalcification is observed, with fractures of the cortex. There are degeneration and fibrosis of the marrow. Magnification, $\times 60$. *B*, the shaft of the rib shown in *A*. Note the extensive resorption of the cortical bone and the fibrosis of the marrow. See *A*. Magnification, $\times 60$. *C*, a section through the middle of the diaphysis of a femur of the guinea-pig from which *A* and *B* were taken. The canals of blood vessels are dilated. Magnification, $\times 60$.

THE APPEARANCE OF OSTEOID TISSUE IN THE BONES OF GUINEA-PIGS GIVEN INTERMITTENT TREATMENT WITH PARATHORMONE

The experiments thus far detailed showed that parathormone produces striking effects on the bones of young guinea-pigs. The changes in the bones observed forty-eight hours after one large dose were so severe as to result in cortical fractures in the regions where the cortex is normally thinnest—that is, at the costochondral junctions and at the metaphyses. Large doses induced in addition, hemorrhage of the marrow, dilatation of the canals of blood vessels and slight fibrosis of the marrow. After repeated smaller doses, extensive fibrosis of the marrow and invasion of the enlarged canals of blood vessels by connective tissue occurred. After both single and repeated administration of parathormone, Howship's lacunae and osteoclasts were numerous.

In none of these experiments in which the treatment was continuous, was there formation of osteoid tissue to any degree. In the experiments in which acute conditions were produced, no osteoid tissue appeared for parathormone produced a constantly progressive resorption of bone which would not permit the formation of osteoid tissue. In the experiments in which chronic changes resulted, the formation of osteoid tissue was not observed except in the reparative process following fracture. It was because of this that we planned experiments in which we gave to some guinea-pigs intermittent treatment with parathormone, for we were desirous of observing the conditions under which extensive osteoid tissue appeared in guinea-pigs treated with parathormone.

Four guinea-pigs, each weighing between 235 and 410 Gm., were subjected to the daily injection of parathormone, beginning with a small dose, which was increased to 20 units by the fourth day. Treatment was continued with this dose until the seventh day. The treatment was then interrupted for seven days. On the fifteenth day it was resumed with the injection of 20 units daily until the twenty-first day in two animals and until the twenty-fourth day in the other two. The treatment was then again discontinued for five or six days. On resumption, the dosage was 20 units for one day, 30 units for one day, 40 units for two days and 60 units for one day. The treatment was discontinued, and the animals were killed after intervals of from three to seven days after the last injection.

One of the most striking features observed in connection with these animals was that the serum calcium of two of them was 8 and 7.4 mg per hundred cubic centimeters. The guinea-pig which was allowed to live for seven days after the last injection of parathormone showed 10.2 mg of serum calcium per hundred cubic centimeters. Two other guinea-pigs, not included in this series, which were also given inter-

mittent treatment, the dosages of which were stepped up to 50 units a day, and which were killed five days after the last injection of parathormone, showed 7.6 and 8.8 mg of serum calcium per hundred cubic centimeters.

An examination of the bones of these animals suggested an explanation of the low serum calcium. Because of the large doses of para-

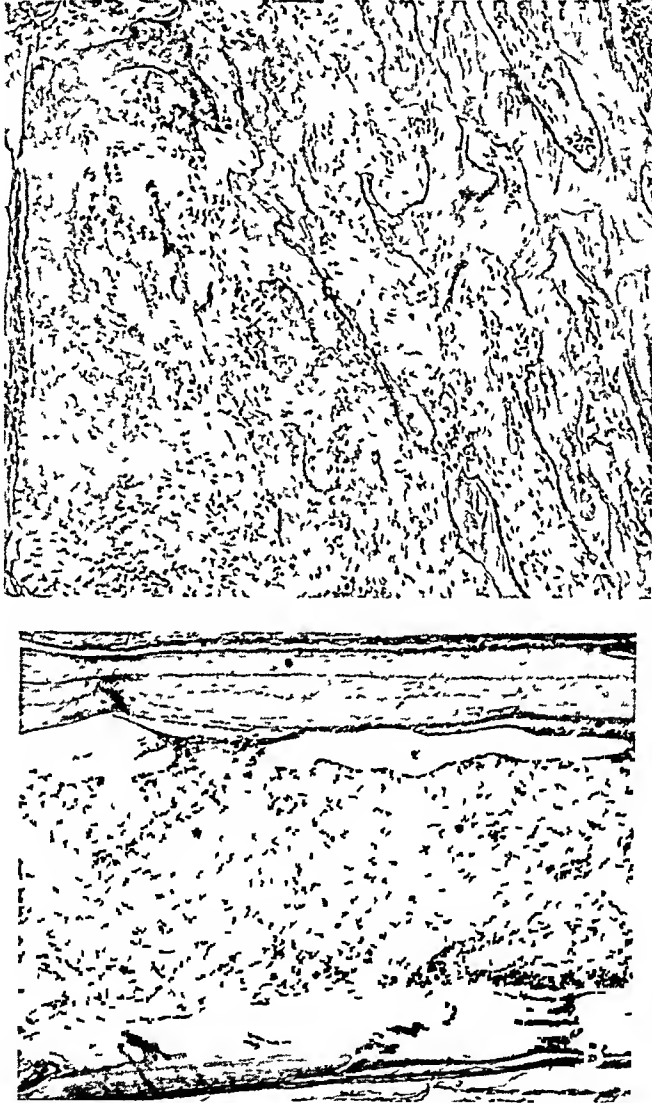


Fig 6—*A*, the shaft of a long tubular bone of a guinea-pig weighing 351 Gm. The animal was given intermittent treatment with parathormone and killed five days after the last injection. Note the extensive fibrosis of bone and the subperiosteal callus formation. Magnification, $\times 60$. *B*, a rib of a guinea-pig given intermittent treatment with parathormone and killed four days after the last injection. There is hemorrhage of the marrow, with fibrosis and multiple cysts, some of which contain blood. Magnification, $\times 60$.

thormone injected during the last few days of the treatment, extensive decalcification occurred, resulting in numerous fractures. A period of

active repair followed after the administration of parathormone had been discontinued, resulting in rapid and excessive deposition of calcium. This demand for calcium for purposes of bone repair may have been the cause of the lowered serum calcium.

During the period of repair the rate of formation of new bone, as demonstrated histologically, was rapid and the amount of new bone extensive. There was extensive subperiosteal callus formation, considerable new bone on the walls of the canals of blood vessels and considerable osteoid tissue at the costochondral junctions and in the metaphyses.

One of the animals showed numerous cysts in the marrow as a result of the extensive destruction of bone and marrow, and these cysts

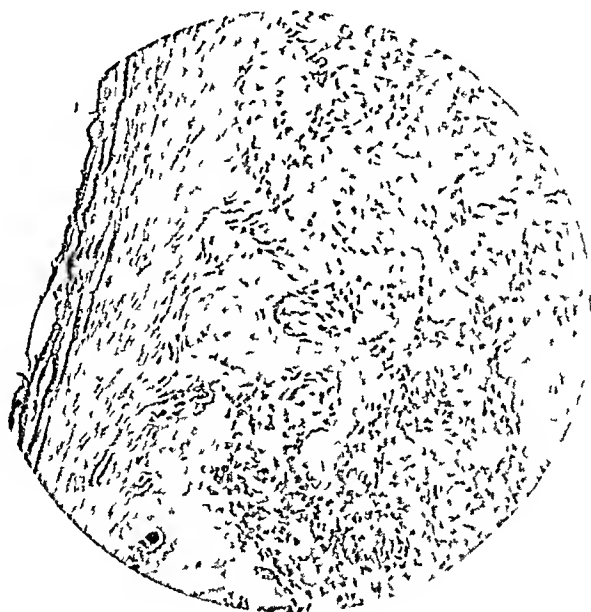


Fig 7—The shaft of a long tubular bone, with considerable osteoid tissue repair, in the same animal from which *B* in figure 6 was taken. Magnification, $\times 130$.

could frequently be identified as dilated vascular spaces secondary to the disturbance in the circulation in the marrow. Cysts and osteoid tissue (see figs 6 and 7) were observed only in those animals that were allowed a few days to recover from the last dose of parathormone. It is therefore to be concluded that the formation of osteoid tissue and that of cysts, in the course of osteitis fibrosa, are features characteristic, not of the lesion produced by hyperparathyroidism, but of the repair of the lesion. The same conclusion regarding osteoid tissue in experimental and clinical hyperparathyroidism was reached by us as a result of our study of hyperparathyroidism in dogs.¹

COMMENT

These experiments have shown that large doses of parathyroid extract (parathormone Collip) injected into young growing guinea-pigs cause severe lesions of the bones. The subcutaneous injection of one large dose of parathormone, 20 units per hundred grams of body weight, into young guinea-pigs produces destructive changes in their bones, and these lesions are characterized by resorption of bone (often very severe), fibrosis of bone, degeneration and fibrosis of marrow and cessation of the formation of bone at the zones of active growth. These lesions could not be definitely discerned before the twelfth hour, after which they progressed rapidly to the forty-eighth hour, and probably went on to repair after that. Extensive repair by subperiosteal formation of callus and production of osteoid tissue was found four days after the last injection of parathormone.

A striking observation in these young guinea-pigs given a large single dose of parathormone was that while ingestion of food was an important factor in moderating the effects of the injections of parathormone on the serum calcium and phosphorus,³ the severe effects on the bones of young animals were present irrespective of fasting or feeding.

In contrast with the young, growing guinea-pigs, the fasting or fed adult guinea-pigs did not suffer appreciable histologic changes in the bones on injection of parathormone (20 units per hundred grams of body weight). However, there was a slight effect of the administration of parathormone on the serum calcium of these animals, more evident in the fasting adult animals. Whether the dosage for the adult animal was relatively too small or whether the bone of the adult guinea-pig resists decalcification by parathormone in any dosage, we are not in a position to state at present. The problem of the effects of parathormone on adult guinea-pigs will be discussed in another paper.

After repeated injections of from 10 to 20 units of parathormone daily for about two weeks histologic examination of the bones of young, growing guinea-pigs showed slight, but definite, resorption of bone and fibrosis of bone and marrow, although no clear effects had been observed on the serum calcium and phosphorus. After thirty-four days of treatment, a more definite effect on the bone and marrow was obtained, accompanied by a definite rise in the serum calcium and by normal phosphorus levels.

Animals receiving repeated large or moderate doses of parathormone all showed extensive lesions of the bones. Those receiving very large doses without having had preliminary treatment with parathormone showed destructive lesions in the bone and bone marrow. Extremely large doses of parathormone could be administered daily to guinea-pigs without the development of an overdosage complex, if

smaller or gradually increasing doses had been administered previously. Guinea-pigs were thus able to survive and maintain their weight for longer periods on large doses. Such animals showed resorption of bone and fibrosis of bone and marrow, but did not show the acute necrosis of marrow and the acute decalcification of bone that were observed in animals given one large dose or repeated large doses without preliminary treatment.

The question arises whether the lesions observed after daily injections of parathormone into guinea-pigs are to be designated as osteitis fibrosa. The changes observed in our experimental animals were as follows: generalized resorption of bone and enlargement of the canals of blood vessels; numerous Howship's lacunae and osteoclasts on the surfaces of the trabeculae, under the endosteum and periosteum, and on the walls of the canals of blood vessels; sclerotic of the bone marrow and metastatic calcification in the gastric and intestinal mucosa, kidneys, heart, lungs and subcutaneous tissues. No osteoid tissue was observed. These changes are in every respect similar to those reported in the two cases of spontaneous fibrous osteodystrophy in rodents. When the question of the nature of the lesions in these animals was raised by the work of Levy and Pick, the latter concluded, in agreement with others, that osteoid tissue was not necessary for making a diagnosis of osteitis fibrosa. Askanazy was the first to recognize "osteitis fibrosa without osteoid," in a case in man. In our experiments we have been able to show that osteoid tissue in fibrous lesions of the bones of guinea-pigs appears in the repair of the process initiated by hyperparathyroidism. We have found that if the destructive changes have been severe enough, the disturbances in the circulation in the marrow lead to the formation of cysts. We therefore believe that formation of osteoid tissue, hemorrhage of the marrow and formation of cysts occur only as secondary features and are not necessary for making the diagnosis of osteitis fibrosa in our experimental guinea-pigs. We further believe that these secondary features may also be produced experimentally with the same regularity as the primary features of osteitis fibrosa.

It remains to emphasize that the lesions produced in our experimental animals were a specific effect of experimental hyperparathyroidism. We have ruled out prolonged fasting as a factor in the experimental production of the acute changes. In the experiments in which chronic lesions resulted, the question of diet may be disposed of by the simple statement that the guinea-pigs were receiving their usual vegetable diet, which was proved adequate in mineral content and accessory food factors by our experience with untreated controls.

The lesions described were in every case generalized. While easier to study in the ribs, they affected all the bones examined. The changes

were most prominent at the costochondral junctions, in the metaphyses and in the diaphyses. The epiphyses did not show the specific effects of experimental hyperparathyroidism.

SUMMARY

The subcutaneous injection of one large single dose of parathormone into a young guinea-pig produces severe and rapid decalcification of the skeleton within forty-eight hours. Age also seems to be a factor in the production of lesions of the bones after single injections of parathormone. Adult guinea-pigs given injections (20 units per hundred grams of body weight) did not show changes in the bones forty-eight hours after the injection. After repeated daily injections of smaller doses of parathormone, resorption of bone and fibrosis of bone and marrow result. The lesions observed after daily injections of parathormone into guinea-pigs are of the same order as those described for osteitis fibrosa without osteoid tissue in man. Osteoid tissue and cysts in the marrow may appear during the repair of severe lesions in experimental hyperparathyroidism of guinea-pigs.

INVASION OF THE FALLOPIAN TUBE BY OXYURIS VERMICULARIS

REPORT OF A CASE

W J JONES, M D

LA CROSSE, WIS

AND

C H BUNTING, M D

MADISON, WIS

The case here published is presented as adding to the data accumulating which seem to show that the widespread parasite *Oxyuris vermicularis* (or more properly *Enterobius vermicularis*) is not to be dismissed too lightly as of little clinical or pathologic importance

REPORT OF CASE

History—One of us (W J J) was called to see, in his practice, Miss M V, a white woman, aged 22, who complained of a pain in the lower right side of the abdomen, which had begun two days previously, and which was becoming more severe. It was associated with nausea and vomiting.

Several points in the patient's history proved of interest and importance. She stated that for ten years she had been subject to intense perineal and anal itching, worse at night, and that her mother and one brother were similarly affected. About four months previously, the patient had a severe pain low down in the left side of the abdomen, which was worse on walking or on jarring. As this was coincident with the onset of menstruation (which on this occasion was manifested by an excessive flow lasting eight days as against a usual four or five day flow), the pain was attributed to this factor. She said that she had not had venereal infection.

Examination—On examination, the patient was found to have marked tenderness in the lower right abdominal quadrant, with distinct rigidity of the muscles of the right side. There was some tenderness in the lower left quadrant. No masses were palpated. Except for slight diffuse bilateral enlargement of the thyroid gland, the general examination revealed no gross abnormality.

The pulse rate was 95, red blood cells, 4,600,000, hemoglobin, 75 per cent, leukocytes, 11,700, temperature, 99.8 F.

Diagnosis and Operation—A diagnosis of acute appendicitis was made, and appendectomy was performed.

At operation, through a right rectus incision, the acutely inflamed appendix was found coiled on itself in the pelvis, to the wall of which it was bound by light, easily broken adhesions which did not interfere with its satisfactory removal. A large cyst of the right ovary was treated by puncture and removal, the remaining ovarian tissue being left in situ.

The left ovary and fallopian tube were bound down in the pelvis by dense adhesions and were delivered with difficulty. The tube showed a distinct inflam-

matory condition, and its distal half was distended into an abscess about 1 inch (2.5 cm) in diameter. The ovary was enlarged and dense, and apparently contained areas of calcification. Ovary and tube were removed, and the abdominal wound was closed.

Course—Convalescence was without interruption, and the patient was discharged on the fourteenth day.

Four weeks later the patient returned with the complaint of intense midline pain low down in the abdomen. The patient was examined under anesthesia, and

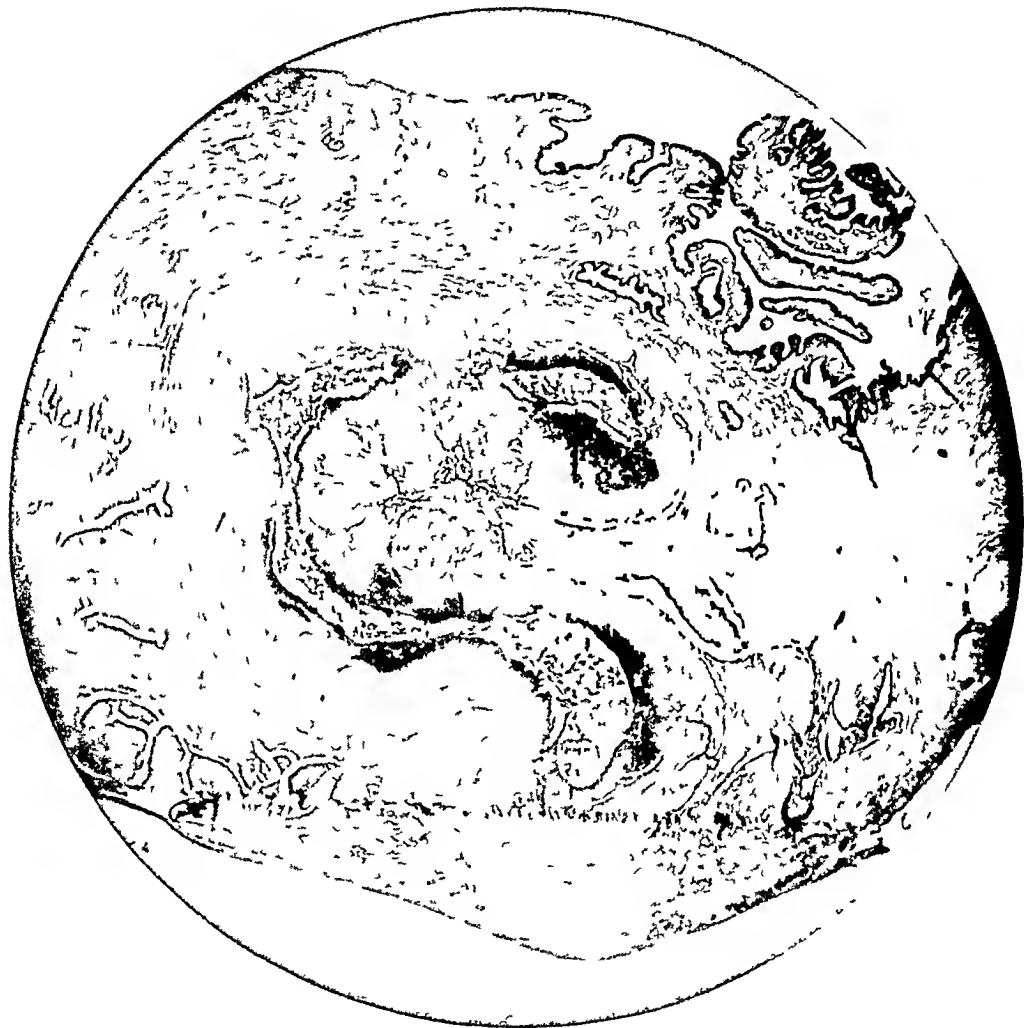


Fig 1—Low power view of the wall of the fallopian tube with invading parasite

there was found an intense inflammation of the vagina with the cervix swollen and eroded in several areas and exuding a slimy discharge. Dilatation and curettage were done.

In the year following this operation, the patient was well and had no recurrence of pelvic symptoms.

Gross Pathologic Examination—The appendix showed a definite acute inflammatory reaction. When opened, it was found to contain several fecal concretions and twenty or more small worms from one-fourth to one-half inch (0.61 to



Fig 2—High power view of a part of the parasite and of the necrotic field surrounding it

1.27 cm) in length. These were alive and active, even after the appendix had been out of the body for some time.

The left fallopian tube showed a marked purulent salpingitis, which converted its distal half into a pus-containing cavity about 1 inch (2.5 cm) in diameter. The wall of the tube was definitely thickened in this area. No worms were found in the exudate.

A part of the thickened wall of the tube was sent to the Pathological Laboratory of the University of Wisconsin for histologic examination.

Histologic Examination of Fallopian Tube—The tubal tissue received in formaldehyde was mounted in paraffin and sectioned perpendicular to the peritoneal surface. As the first section cut showed an area of necrosis suggestive of tuberculous caseation, but without the histology of a tuberculous lesion, a short series of sections was cut in an effort to find the etiologic agent. The finding of the ova of *Oryzias vermicularis* led to further serial sections, until there was disclosed a female oxyurid lying in the wall of the tube and curled on itself, as shown in the low power photograph (fig. 1). The cuticle of the worm was well preserved, but not intact, and the parasite was heavily loaded with ova, as shown in the photograph at higher power (fig. 2). That the defects in the cuticle were not artefacts was shown by the fact that in certain areas there was a marked invasion of the worm by leukocytes, a considerable proportion of which were eosinophils. The parasite was surrounded throughout by a zone of necrosis. The necrotic cells were chiefly leukocytes, although in certain areas there was definite necrosis of tubal tissue. Among the dead leukocytes, there was evidence of a marked eosinophil participation in the exudation. In fact, the living polymorphonuclear leukocytes at the tissue edge of the necrotic zone were almost entirely eosinophil. Mononuclear phagocytes were conspicuously absent. About the zone of necrosis there was well marked connective tissue encapsulation, with a moderate infiltration by lymphocytes, plasma cells and eosinophil leukocytes. The epithelial and peritoneal surfaces of the tubal section were intact. There was an inflammatory dilatation of the vessels beneath the epithelium and some leukocytic and lymphocytic exudation.

The impression was gained that the parasite had burrowed into the tubal tissue along the sulci between the major folds and not directly into the wall at the point where it was found, as no sign of injury was seen in the tissue or in the epithelium immediately over the worm. As shown in figure 1, the oxyurid lay almost equidistant from the epithelium and the peritoneal covering of the tube.

Histologic sections of the ovary showed an atrophic, sclerotic organ with old fibrous adhesions attached to the surface. There was no evidence of further parasitic involvement.

Curettings from the uterus showed a chronic endometritis with definite, extensive fibroblastic proliferation. No lesion was found other than hemorrhage, which was apparently due to the curetting.

SUMMARY

In a woman 22 years old with a history of prolonged perineal nocturnal itching and with symptoms of pain and tenderness in the lower part of the abdomen, accompanied by fever and leukocytosis, there was found at operation (1) acute appendicitis, with many nematodes of the genus *Oryzias vermicularis* in the lumen, and fecal concretions and (2) acute salpingitis, with a female oxyurid embedded

in the wall of the tube. Unfortunately, cultures were not made from the appendix or from the tube and the appendix was not saved for section.

According to Heller,¹ the embryo oxyurids emerge from ova high up in the intestine, develop gradually in their slow progress down the intestine, until, in about two weeks, they reach the cecum in a sexually mature stage. Here and in the appendix conjugation takes place, and the worms remain in these parts longer than in any other part of the intestine. The mature females eventually move gradually down the colon, laying their eggs on fecal masses and on the skin when they wander out of the anus at night. Heller regards the presence of *Oxyuris* in the lumen of the appendix as of no pathologic significance. This would seem to be true. However, as is shown definitely in the reports of Cecil and Buckley,² and of Rheindorf,³ the worm may invade the wall of the appendix and may possibly penetrate even to the serosa. This raises the question of the part played by the worm in initiating appendicitis. Cecil and Buckley concluded from their study that there is a definite and characteristic form of appendicitis produced by *Oxyuris* and *Trichocephalus*. Rheindorf³ was of the same opinion. Aschoff,⁴ in controversy with Rheindorf, took an opposite position and spoke of a "pseudo-appendicitis."

The present case can add no evidence on either side of the controversy, as the appendix was not studied histologically to determine whether or not it was invaded. It would seem from the cases of Weigmann⁵ and Vuillemin⁶ that the worm may penetrate the intestinal wall and either of itself or through bacteria carried with it initiate suppurative processes. Weigmann, in a boy of 6, found on each side of the anal opening a perinectal abscess containing living oxyurids and scattered ova, and Vuillemin quoted his confrere Fieoch as having found in a boy of 11, a perinectal abscess containing sixty female oxyurids. In neither case was gross communication found between the abscess and the intestinal lumen.

Nathan (quoted by Chiarì⁷) reported a somewhat similar case of a young laborer with a perinectal abscess that would not "open" under ordinary treatment. The abscess showed eggs of *Oxyuris* but no bacteria, when examined pathologically after operation.

1 Heller. Deutsches Arch f klin Med **77** 21, 1903

2 Cecil and Buckley. Am J M Sc **143** 793, 1912

3 Rheindorf. Zentralbl f Bakteriöl **74** 604, 1914

4 Aschoff. Berl klin Wchnschr **57** 1041, 1920

5 Weigmann. Berl klin Wchnschr **58** 732, 1921

6 Vuillemin. Zentralbl f Bakteriöl **32** 358, 1902

7 Chiarì. Virchows Arch f path Anat **269** 730, 1928

A similar question arises in regard to the relationship of *Oxyuris* to lesions in the female generative tract. One must assume that the female parasite in its out-wanderings at night gets into the vagina much oftener than references in the literature would suggest. It must commonly therefore not produce lesions there.

That the worm may traverse the whole genital tract and become implanted and encapsulated on the peritoneum without symptoms is definitely indicated by the finding of such nodules accidentally at operation or at postmortem examination. Goodale and Krischner⁸ recently reported such a case and collected from the literature six others, all in women. Their case was in a woman of 21 in whom, in the course of an operation, several loops of the pelvic small bowel were found covered with hard, white nodules, each slightly smaller than a pea. These nodules were diagnosed as tubercles but when one was sectioned it was found to contain a female oxyurid filled with ova.

Marro⁹ reported the occurrence in a woman of 34 of a cyst implanted on the fallopian tube near the fimbriated extremity. This had a wall 2 mm thick and contained the ova of *Oxyuris*, granular detritus and cholesterol crystals.

In a 42 year old woman who had died of cancer of the breast, Kolb¹⁰ found ten nodules of the size of a grain of rice scattered in the pelvic peritoneum. One of these on section showed a female oxyurid surrounded by granular detritus, giant cells and a connective tissue capsule.

Schneider¹¹ found in the culdesac of a 36 year old patient who had died of peritonitis after a hysterectomy an encapsulated cyst 2 cm in diameter which contained a female worm.

Strada¹² found an encapsulated oxyurid in the culdesac of a woman of 60 who had died of bronchopneumonia.

Schroeder¹³ is quoted by Chauri as having seen a similar case.

Kaufmann's¹⁴ case of ova of *Oxyuris* in one of numerous caseous nodules seen on the colon and mesocolon of a woman of 31, at an abdominal operation is perhaps not so clearly an infestation of the peritoneum by the genital route.

In all of these cases there was set up a sharply localized inflammatory reaction resulting eventually in encapsulation, and in no case was there

8 Goodale and Krischner Arch Path **9** 631, 1930

9 Marro Gior d r Accad di med di Torino **7** 251 1901

10 Kolb Zentralbl f Bakteriöl **31** 268, 1902

11 Schneider Zentralbl f Bakteriöl **36** 550, 1904

12 Strada, quoted by Goodale and Krischner (footnote 8)

15 Tschamer Zentralbl f Gynak **43** 989, 1919

14 Kaufmann Pathology for Students and Practitioners (Reimann's translation of Lehrbuch der pathologischen Anatomie), Philadelphia, P Blakiston's Son & Company, 1929, vol 2, p 855

a general peritoneal reaction. In none of these cases was there note of pathologic effects in the uterus or in the tube.

Tschamer's¹⁵ finding of two living worms in the fallopian tube at total hysterectomy for chorionic epithelioma in a patient of 31 without evidence even histologically of local reaction, confirms the possibility of a passage of the worm without the production of lesions.

We have been able to find in the literature only two references to invasion of the wall of the tube by *Oxyuris*—the case of Strasser and that of Chiani.

Strasser's¹⁶ case was that of a woman of 26 with tuberculous peritonitis in the wall of whose fallopian tube there were found calcified masses, singly in clumps and in long packets. These were surrounded by foreign body giant cells and there was a marked fibrous alteration of the wall of the tube adjacent to them. When decalcified, these masses were found to be ova of *Oxyuris*. The reaction here was evidently similar to that in the peritoneum.

Chiani's⁷ case corresponds closely with that reported here. A young woman of 20 who had had symptoms of pelvic inflammation six months previously was seized suddenly with sharp pain low in the abdomen and had fever and vomiting but no vaginal discharge. Tenderness in the right side on pressure led to a diagnosis of right salpingitis and to operative removal of that tube. Examination of the tube showed a swelling to 4.5 cm. of the distal portion with a hard, scarlike thickening of the wall, a milky, purulent, blood-tinged content and light peritoneal adhesions. In section, there was encountered a female oxyurid partly in a cyst and partly embedded in the mucosa of the tube—with a definite zone of necrosis about it, and with a sharp eosinophil reaction, corresponding clearly to the reaction in this case. No cultures were made, but no bacteria were found in smears of the tubal exudate or in section. Chiani expressed the opinion that the worm was responsible for the salpingitis.

It would seem that we might conclude from our case and those reported in the literature, that *Oxyuris vermicularis* may be present in the lumen of the appendix or in that of the genital tract in women without producing definite lesions or symptoms, but that on invasion of the wall of any viscus it may be responsible for a definite inflammatory reaction in which exudation of eosinophil leukocytes is a prominent feature. Ordinarily, encapsulation ensues. Occasionally, a suppurative process results. Whether the latter lesion is due entirely to *Oxyuris* or in part to associated bacteria is not definitely determined by the cases thus far reported.

15 Tschamer Zentralbl f Gynak 43 989, 1919

16 Strasser Inaugural Dissertation, Bonn, 1915

MAMMARY GLAND SITUATED ON THE LABIUM MAJUS

REPORT OF A CASE *

JOSEPH McFARLAND, M D
PHILADELPHIA

In March, 1930, A. R., a colored woman, aged 34, married, who had progressed about six months in her third pregnancy, was admitted to the psychopathic ward of the Philadelphia General Hospital, in the service of Dr. Max H. Bochroch. She was not long in the ward before it was discovered that she had a rounded, pendulous body attached by a broad and not long pedicle to the lower third of the right labium majus. The general surface of the skin covering it was smooth and without hairs. Pressure showed the body to be slightly sensitive. The patient was carefully questioned as to the duration of the lesion, but her mental state was such that none of her statements could be considered as without great probability of error. She, however, asserted that it had made its appearance shortly after the beginning of the present pregnancy, never having been recognized before.

After careful examination and consideration, the diagnosis of fibroma of the vulva was reached. The intern, Dr. Joseph Parrish, was authorized to remove it, which he did on March 19, 1930.

The tissue received at the laboratory measured 5 by 3 by 2.5 cm. It was covered with deeply pigmented skin (the patient was a rather dark Negress) that had retracted into folds. Beneath the skin was an encapsulated node, so loosely attached that it seemed to be separating itself from its surroundings. It seemed to consist of several lobulations.

When cut through, the structure was the same throughout and appeared coarsely granular and porous, so that the diagnosis was changed from fibroma to adenoma. There was a peculiar pale yellowish color that seemed to be the result of the glandular substance, which was yellowish, alternating with pinkish-white stroma.

Microscopic sections were prepared and were expected to show adenoma of Bartholin's gland, but instead showed typical mammary tissue of advanced pregnancy. The yellowish tinge was found to

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From the McManes Laboratory of Pathology of the University of Pennsylvania and the Pathological Laboratory of the Philadelphia General Hospital.

be caused by the considerable quantity of fat in the vacuolated secretory cells

The gross appearance of the interesting abnormality is shown in the accompanying drawing, a sketch made by Dr. Parrish, who performed the operation. Photomicrographs of the sections under low and high power lenses are also shown. Photomicrographs, under the same magnifications of sections from the normal pectoral mamma of a woman



Fig 1—Drawing of mammary gland situated on the labium majus, at the sixth month of pregnancy

at the same stage of pregnancy were compared, and the resemblance of these to the two was such that in arranging the latter for publication it was necessary to refer to the numbers published on the photographs in order not to confuse them

I communicated my interest in this rare malformation to Dr. Bochi, who gave me the specimen, together with the necessary data and permission to publish a report of the case. Dr. Parrish supplied the sketch

As is well known, the milk lines run diagonally from the axillary to the pubic regions, many mammary rudiments appearing in the embryos of all mammals, to be developed or suppressed according to the phylogenesis of the particular group under consideration. In man, all are normally extinguished, except one on each side in the pectoral region, in the cetacea, all disappear, except one on each labium majus vulvae. When suppression of any of the rudiments fails, supernumerary mammae develop. In this case one of the rudiments so placed as later to be



Fig 2—Section of the vulvar mamma described in this report

situated on a labium majus survived, with the occurrence of a mammary gland in a rare situation

The case is, however, not unique. Hartung¹ described what appears to be the first case published. The subject was a woman, aged 30, to the lower inner aspect of whose left labium majus a body the size of a goose egg was attached by a pedicle the size of a man's thumb. It was congenital. It had enlarged at puberty, was wont to manifest changes coinciding with the menstrual periods and exuded a milky fluid from an eroded area on the upper anterior surface, where careful examination

¹ Hartung. Inaugural Dissertation, Erlangen, 1872

revealed a retracted nipple surrounded by a shallow depression. It was removed and, when examined microscopically, proved to be a fully developed mammary gland.

De Blasio² observed a young woman who had a mammary gland the size of a hen's egg on the outer side of each labium majus, surmounted

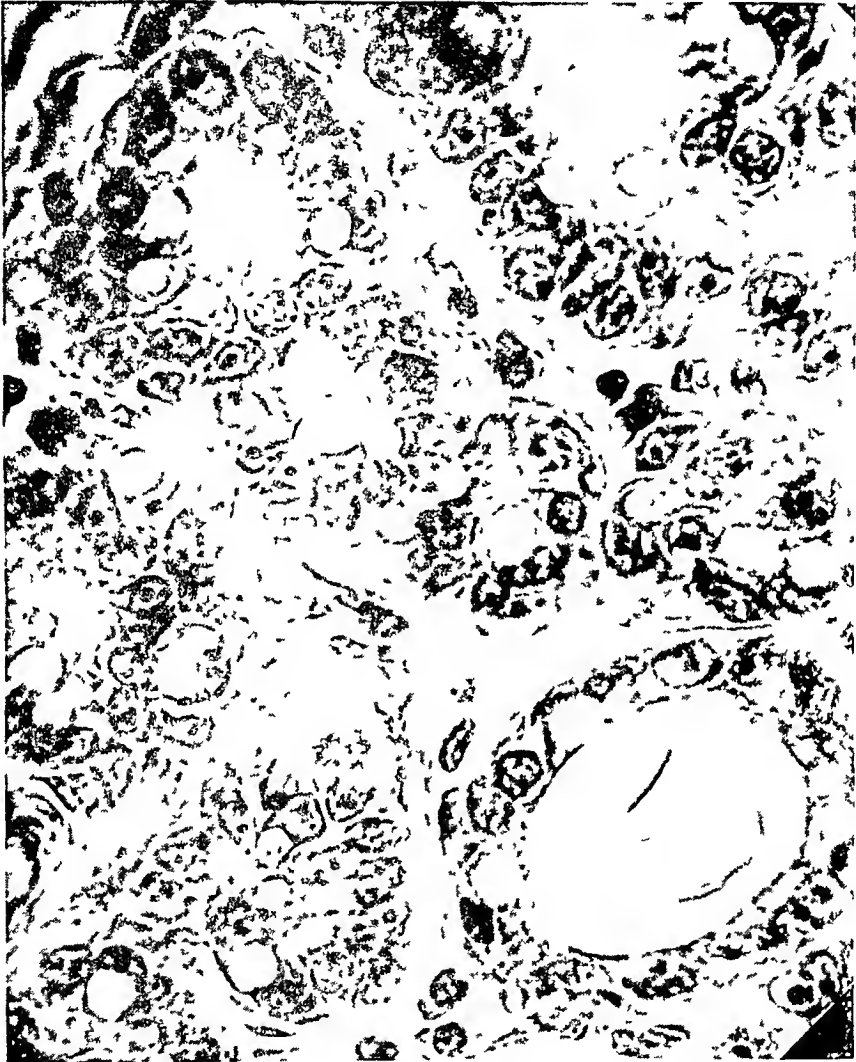


Fig. 3—Section of the vulvar mamma magnified to show the fat vacuoles in the cells and jelly-like cylinders caused by the coagulation of proteins in the colostrum being condensed by the fixative—a picture identical with that of a similarly magnified section of normal pectoral mamma of a woman about eight months pregnant.

by a well formed nipple. To the age of puberty only the nipples were visible, the glands developing later. It was during pregnancy that the maximum size and development were reached.

² de Blasio. *Arch. di psichiat.*, Torino **24**, 171, 1905.

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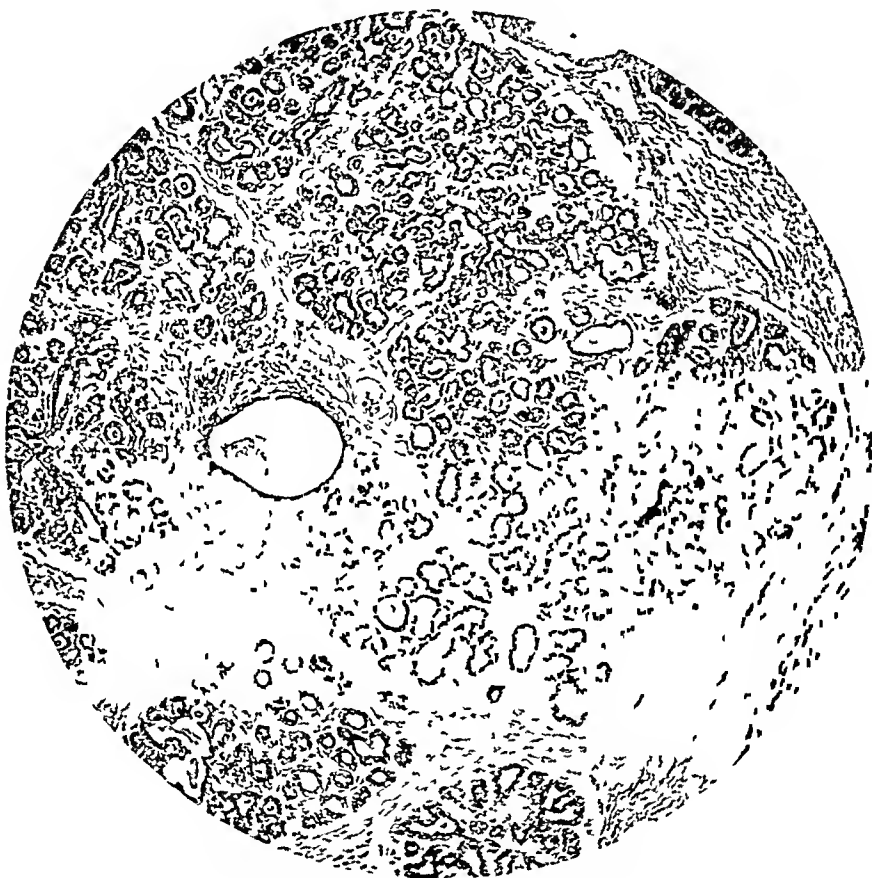


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² de Blasio Arch. di psichiat., Torino 24 171, 1905

Bell³ reported the case of a multipara, aged 59, who had a body the size of a hen's egg attached just in front of the left labium majus by a pedicle 3 cm in diameter. It was of variable consistency, elastic and unattached to the skin that slid over it easily. When removed and examined microscopically, it showed a structure identical with the resting mammary gland.

The case herein reported seems, therefore, to be the fourth noted occurrence of this rare anomaly.

It is unfortunate that the patient suffered from mental disturbance, as it prevented us from learning how the gland behaved in her earlier pregnancies. Theoretically, it should have evolved and retrogressed with each

³ Bell. *Am J Obst & Gynec* **11** 507, 1926

THE RESPONSE OF BLOOD PLATELETS TO EXTERNAL STIMULI ULTRAVIOLET LIGHT, IODINE AND COAL TAR

PAUL E STEINER, M S

AND

FRANCIS D GUNN, M D

CHICAGO

The number of blood platelets in healthy animals is fairly constant, though daily and even hourly fluctuations of considerable volume occur. In general, the level is not as constant as that of erythrocytes, but is more constant than that of leukocytes. Spontaneous variations, when they occur, can usually be explained on the basis of infections or of alterations of the environment, especially changes in light. In experimental procedures devised to study the problems of the origin and the function of the blood platelets a great variety of agents have been employed for altering the platelet content of the blood. Recently, some of these methods have been used clinically in man in attempts to influence the course of disease in which the number of platelets has been pathologically altered.

The effective agents can be divided roughly into internal and external. The former, including toxic and irritating substances, especially bacterial toxins introduced into the blood stream, intravenous injections of particulate matter, infections, splenectomy and hemorrhage, have been studied extensively by numerous workers. The latter, consisting chiefly of the different forms of radiant energy, have received but little attention until recent years.

In 1913, Duke¹ studied the effects of benzene and diphtheria toxin and found that with fatal doses the number of circulating platelets was decreased while with nonfatal doses their number was increased. Large doses of tuberculin were necessary to produce a similar response. Weiskotten, Wyatt and Gibbs² and Hultgren³ corroborated his results.

* Submitted for publication, Aug 12, 1930

¹ From the Department of Pathology, Northwestern University Medical School

1 Duke, W W Causes of Variation in the Platelet Count, Arch Int Med **11** 100, 1913

2 Weiskotten, H G, Wyatt, T C, and Gibbs, F R D The Action of Benzol VII Thrombocytopenia and Thrombocytosis Coincident with Marrow Necrosis and Marrow Regeneration (Rabbit), J M Research **44** 593, 1924

3 Hultgren, G Action du benzol sur la teneur du sang en thrombocytes, leucocytes et erythrocytes, Compt rend Soc de biol **95** 1060, 1926

with benzene. Many earlier authors, and more recently Bannerman,⁴ found an increased platelet count in pulmonary tuberculosis, the higher levels occurring most commonly in the progressive cases.

In 1915 Duke⁵ stated that the platelets are usually decreased in number during the febrile stage of acute infectious diseases and increased in number during convalescence. Reimann,⁶ in studies of the behavior of blood platelets during the course of pneumonia in man, and in experimentally infected rabbits, found that thrombopenia occurs during the febrile period, and that the normal number is greatly exceeded during the postfebrile period following the crisis.

Particulate matter introduced into the blood stream sometimes produces a rise and sometimes a fall in the number of platelets. Suspensions of killed bacteria (Duke⁵) and carbon particles (Bedson⁷) have been found to produce considerable increases. Beronius,⁸ Koster⁹ and Cramer and Bannerman¹⁰ reported increases in platelets following the injection of trypan blue. Injections of colloidal lead (Brookfield¹¹), india ink (Bedson⁷) and many other agents of a particulate nature have been reported as effective in increasing the number of blood platelets.

That sudden, severe hemorrhage is followed by a rapid regeneration of platelets was demonstrated in 1911 by Duke¹² and corroborated later by Petri¹³.

4 Bannerman, R. G. Blood Plate Counts in Pulmonary Tuberculosis, *Lancet* **2** 593, 1924.

5 Duke, W. W. Variation in the Platelet Count, Its Cause and Clinical Significance, *J. A. M. A.* **65** 1600, 1915.

6 Reimann, H. A. A Study of the Behavior of Blood Platelets in Pneumococcus Infections, *J. Exper. Med.* **40** 553, 1924.

7 Bedson, S. P. The Role of the Reticulo-Endothelial System in the Regulation of the Number of Platelets in the Circulation, *Brit. J. Exper. Path.* **7** 317, 1926.

8 Beronius, H. Action du bleu trypan sur la formule sanguine du lapin, *Compt. rend. Soc. de biol.* **99** 1675, 1928.

9 Koster, H. Reticulo-Endothelial System Platelets, *J. Exper. Med.* **44** 75, 1926.

10 Cramer, W., and Bannerman, R. G. Clinical Significance of Blood Platelets, *Lancet* **1** 992, 1929.

11 Brookfield, R. W. Blood Changes Occurring During the Course of Treatment of Malignant Disease by Lead, with Special Reference to Punctate Basophilia and the Platelets, *J. Path. & Bact.* **31** 277, 1928.

12 Duke, W. W. The Rate of Regeneration of Blood Platelets, *J. Exper. Med.* **14** 265, 1911.

13 Petri, S. III Experiments by a Special Bleeding Technique to Produce Isolated Influencing of Blood Platelets and Their Source, *Acta path. et microbiol. Scandinav.* **2** 23 and 277, 1925.

Myers and his associates,¹⁴ Evans,¹⁵ Washburn¹⁶ and many others have reported increased numbers of blood platelets after splenectomy. Bachman and Hultgren¹⁷ also found an increase after splenectomy, but obtained similar results by traumatizing the mesentery and putting sutures into it. Liles¹⁸ observed a rise after operative procedures. Dawbarn and his associates¹⁹ counted platelets in a large series of cases in the hospital and found their numbers increased after operations of all kinds, childbirth and fractures. They suggest that the common factor is injury to tissue with absorption of the products of protein disintegration.

Binet and Kaplan²⁰ observed that after asphyxia in dogs the platelet level was elevated for about an hour. This did not occur if splenectomy had been previously performed. Epinephrine (Binet and Kaplan²¹), given to cause contraction of the spleen, produced a similar rise. The rise did not occur after splenectomy or after the administration of yohimbine to prevent contraction of the spleen.

The external agents studied have consisted chiefly of different forms of radiant energy—sunlight, x-rays and radium emanations.

Cramer, Drew and Mottram²² found that large doses of radium produced a decided fall in the number of platelets. Fabricius-Moller²³

14 Myers, B., Mangot, R., and Gordon, A. K. Three Cases of Splenectomy for Essential Thrombocytopenic Purpura Hemorrhagica, *Proc Roy Soc Med (Clin Sect)* **19** 37, 1926.

15 Evans, W. H. The Blood Changes after Splenectomy in Splenic Anemia, Purpura Hemorrhagica and Acholuric Jaundice, with Special Reference to Platelets and Coagulation, *J Path & Bact* **31** 815, 1928.

16 Washburn, A. H. Splenectomy in Thrombocytopenic Purpura, *J A M A* **94** 313, 1930.

17 Bachman, E. L., and Hultgren, G. Influence de l'intervention chirurgicale en particulier de l'extirpation de la rate sur la teneur du sang en thrombocytes, *Compt rend Soc de biol* **94** 942, 1926.

18 Liles, R. T. Blood Platelets in Rabbits Following Splenectomy and Transplantation of the Spleen, *Proc Soc Exper Biol & Med* **23** 489, 1926.

19 Dawbarn, R. V., Erlam, F., and Evans, W. H. The Relation of the Blood Platelets to Thrombosis after Operation and Parturition, *J Path & Bact* **31** 833, 1928.

20 Binet, L., and Kaplan, M. Mobilisation des plaquettes par l'asphyxie. Origine splénique de la plaquettose asphyxique, *Compt rend Soc de biol* **97** 1128, 1927.

21 Binet, L., and Kaplan, M. Mobilisation des plaquettes par l'adrenaline. Plaquettose par spleno-contraction adréalinique, *Compt rend Soc de biol* **97** 1659, 1928.

22 Cramer, W., Drew, A. H., and Mottram, J. C. Similarity of Effects Produced by Absence of Vitamines and by Exposure to X-Rays and Radium, *Lancet* **1** 963, 1921.

23 Fabricius-Moller, A. Études expérimentales sur la diathèse hémorragique déterminée par les rayons Roentgen, *Compt rend Soc de biol* **87** 759, 1922.

reported thrombopenia from massive doses of x-rays Mottram²⁴ observed transitory thrombocytosis after smaller doses of radium Cramer and Drew²⁵ showed that rats kept in darkness from birth had a lower platelet count than those reared under normal light conditions, and in these rats, exposure to the mercury vapor quartz lamp for short daily periods caused the platelet level to rise rapidly toward normal Laurens and Sooy²⁶ found that growing albino rats had a lower platelet count at the end of six months if kept in darkness than if exposed to diffuse daylight or to direct sunlight Sooy and Moise²⁷ treated ten patients suffering from purpura with the mercury vapor quartz lamp, and observed increases in the number of blood platelets and abatement of symptoms In one case, the platelet count increased from 108,000 to 546,000 Gunn,²⁸ working with young rabbits, exposed the shaved back daily to the mercury vapor quartz lamp and found a temporary increase in the platelet count Miles and Laurens²⁹ showed that in dogs kept in darkness the number of platelets was lowered and that there was a rise above normal followed by a gradual return to normal when the animals were returned to light They then tried the effect of carbon arc radiation and obtained an increase in the platelets after temporary depressions Hardy³⁰ repeated and extended the experiments of Gunn on rabbits, carefully measuring the intensity and the wave length of the light used Sanford³¹ studied the effect of ultraviolet light on infants 4 days old, and found that the number of platelets was temporarily increased Mayerson and Laurens³² found a slight rise

24 Mottram, J C Some Effects of Exposure to Radium on the Blood Platelets, *Proc Roy Soc Med (Sect Path)* **16** 9, 1923

25 Cramer, W, and Drew, A H The Effect of Light on the Organism, *Brit J Exper Path* **4** 271, 1923

26 Laurens, H, and Sooy, J W The Effect of Light and of Darkness on the Blood Cell Count of the Growing Albino Rat, *Proc Soc Exper Biol & Med* **22** 114, 1924

27 Sooy, J W, and Moise, T S Treatment of Idiopathic Purpura Hemorrhagica, *J A M A* **87** 94, 1926

28 Gunn, F D The Influence of Ultraviolet Light upon Blood Platelets in Young Rabbits, *Proc Soc Exper Biol & Med* **24** 120, 1926

29 Miles, A L, and Laurens, H III The Effects of Darkness on Some of the Physical Characters of the Blood of Dogs, *Am J Physiol* **75** 443, 1926, IV The Effects of Carbon Arc Radiation on Some of the Physical Characters of the Blood of Dogs, *Am J Physiol* **75** 462, 1926

30 Hardy, M The Effect of Measured Amounts of Ultraviolet Radiation on the Blood Count of Normal Rabbits, *Am J Hyg* **7** 811, 1927

31 Sanford, H N Effect of Ultraviolet Light on the Blood of New-Born Infants, *Am J Dis Child* **33** 50, 1927

32 Mayerson, H S, and Laurens, H The Effect of Carbon Arc Radiation on the Blood of Dogs, *Am J Physiol* **86** 1, 1928

following exposure to the carbon arc in dogs, which persisted for about ten days Vannfalt³³ corroborated the work of Gunn on rabbits, and also observed an increase in the human being treated with ultraviolet rays³⁴ This increase varied greatly with dosage and individual susceptibility

The mechanism by which the radiation causes a rise in blood platelets is not understood The evidence furnished by experiments with darkness and sunlight and the results reported recently by Phillips and Robertson³⁵ with feeding of viosterol indicate a photochemical effect in the skin, possibly by the action of light on lipoids in the skin On the other hand, the almost constant occurrence of thrombocytosis after operative procedures involving trauma to tissues would suggest that the effect might be brought about by the absorption of products of the destruction of tissue at the site of injury (i e., in the skin), and that these products may be the effective stimuli for the production of platelets

The experiments reported in this paper were suggested by an observation made during the course of an experiment with ultraviolet light It was noticed that the platelet count was sometimes increased after the animal's back was shaved preliminary to treatment with the ultraviolet lamp, particularly if the skin was lacerated This suggested that it might be advantageous to investigate the effects on the blood platelet level, of various irritants applied locally to the skin By this means it was hoped that some information might be obtained with regard to the specificity of the effects of ultraviolet light and possibly with regard to the nature of the stimulus or stimuli competent to affect generation of platelets This paper will describe alterations in the blood picture coincident with inflammatory reactions in the skin of young rabbits, produced by ultraviolet light and by local applications of iodine and of coal tar

NORMAL BLOOD COUNTS OF RABBITS

Before experimental alteration of the number of the blood platelets was attempted, the formed blood elements were counted daily for several days in order to establish the normal level for each animal

Method—Fourteen miscellaneous stock rabbits, varying in weight from 980 to 2,915 Gm, were used for the experiments Blood counts were made daily at approximately the same hour The method used for counting platelets was an

33 Vannfalt, K A Action des rayons ultraviolets sur la teneur du sang du lapin en leucocytes et en thrombocytes, *Compt rend Soc de biol* **101** 607, 1929

34 Vannfalt, K A Action de la lumière ultraviolette sur la composition du sang humain, *Compt rend Soc de biol* **101** 610, 1929

35 Phillips, R A, and Robertson, F D Effect of Irradiated Ergosterol on Mammalian Thrombocyte Counts, *Proc Soc Exper Biol & Med* **26** 639, 1929

indirect one in which stained films were used (Gunn and Vaughan³⁶) The blood films were stained with Wright's blood stain, covered with oil and cover-slip and counted under the high power, dry lens A minimum of 1,000 erythrocytes was counted, with the platelets in the corresponding fields From this ratio of platelets to erythrocytes the total number of platelets per cubic millimeter was calculated Leukocyte and erythrocyte counts were made at the same time by the usual methods Whenever there was a marked change in any of the elements, that count was repeated at once with a new blood specimen

The animals were fed on the standard laboratory diet of carrots, oats and water daily, and alfalfa two or three times a week The pens were kept in room light, but out of direct sunlight The rectal temperature was taken daily and the weight frequently

Results—For periods of from four to eleven days preceding the experiment proper, the average for the group of fourteen rabbits was 980,000 platelets per cubic millimeter There was considerable difference in the different animals, the lowest average was 626,000 and the highest, 1,619,000 In one case the daily variation was as much as 60 per cent The animals exhibiting the highest platelet levels showed the greatest daily variation in counts

The leukocyte average for this group was 11,051 per cubic millimeter Here, also, there was considerable daily variation The averages for the control period were between 6,450 and 14,867 Occasional high counts were found for one day, but were unaccompanied by any rise in temperature Bachman and his associates³⁷ found that when the platelet level was high, the leukocyte count also was high We were unable to find any such correlation in our counts

The erythrocyte average was 5,961,780 for the series The variation in different animals was between 5,120,000 and 6,836,000 The level in individual animals is rather constant However, if water is withheld or for any reason the rabbits refuse to take food and liquids, they may become quickly dehydrated with a correspondingly rapid rise in the erythrocyte count

Comment—These results emphasize the necessity for studying carefully the platelets of any given rabbit for an adequate period of time prior to any experimental procedure, in order to establish the normal variation for this animal Even then the results must be interpreted with caution Considerable variation is to be expected in the rabbit Binet and Kaplan²¹ showed that after injections of epinephrine to cause contraction of the spleen, there may be a 100 per cent increase in the number of circulating platelets, persisting for about one hour It is

36 Gunn, F. D., and Vaughan, S. L. Bone Marrow Reactions. II. The Blood Count in the Albino Rat. Blood Platelets, *Anat. Rec.* **45**: 59, 1930

37 Bachman, E. L., Edstrom, G., Grahs, E., Hultgren, G., and Price, H. Teneur du sang du lapin en plaquettes et en globules blancs, *Compt. rend. Soc. de biol.* **91**: 1089, 1924

known that the spleen contracts in times of emotional excitement, so that fright in the animal during the collection of the blood specimens might cause considerable variation in susceptible animals

Comparison of the platelet counts in rabbits by different writers shows great differences. Duke¹ gave the average for eighteen rabbits as 757,000 and mentioned that environmental changes cause 50 per cent variation. Bachman and his associates² in 127 counts on sixty-seven adult rabbits reported a maximum of 870,000 and a minimum of 450,000 platelets per cubic millimeter with an average normal variation of from 13 to 17 per cent. Pett³ gave the average as 714,866 and Liles¹⁸ as 375,000. Gunn²⁸ reported a variation of from 1,040,000 to 700,000 in young rabbits. The results obtained in this series are closest to those of Duke and of Gunn.

EFFECT OF ULTRAVIOLET LIGHT ON BLOOD COUNTS

Method—Five albino rabbits weighing from 1,255 to 2,915 Gm. were exposed daily for periods of from three to five days at a distance of 16 inches (40 cm). Exposures of four minutes were used as initial doses, and these doses were increased to twenty minutes in four animals and to forty minutes in two. The source of radiation was the mercury vapor quartz lamp (Victor, 110 volts, 10 amperes). Platelet, leukocyte and erythrocyte counts were made daily for periods of from five to nine days before the radiation was begun, then the animals' backs were shaved over an area about 10 by 12 cm. It was noticed that in one case an appreciable rise in the platelets followed shaving, the skin having been lacerated superficially in several places. Thereafter the backs were closely clipped with scissors, but not shaved, and counts made in each case for about five days longer to exclude this procedure as a factor. The animals, with one exception, were killed at about the time of the maximum platelet level or soon afterward.

Results—Table 1 shows a brief summary of results in this series, and chart 1 represents graphically a typical platelet curve with ultraviolet light. Analysis of the results shows some fluctuation of the erythrocytes count which bears no definite time relationship to the experimental procedure. The leukocyte counts vary greatly, each rabbit showing at least one high leukocyte count, but the variations seem to be entirely unrelated to the experimental treatment. The temperature was not elevated during these sudden leukocytic increases, furthermore similar increases appeared in two rabbits in the absence of any experimental procedure. Changes in temperature were insignificant at all times. The weight tended to fall slightly during the course of the irradiation.

The blood platelets showed a definite increase in number in three rabbits and no change in two. The increase percentages in R46, R48 and R49 were 163 per cent, 81 per cent and 59 per cent, respectively. The increase began in from twenty-four to seventy-two hours after the

TABLE 1—*Influence of Ultraviolet Light on Number of Blood Platelets*

Rabbit	Weight, Gm	Platelets			Platelet Increase, per Cent	Expo- sures*	Time, Min
		Normal Average	Normal Maximum	Experimental Maximum			
46	1,710	760,000	828,000	2,000,000	163	5	5-15
47	1,625	1,062,000	1,562,000	861,000		3	7, 10, 15
47	2,755	792,000	913,000	984,000	24	7	7-40
48	1,918	732,000	872,000	1,323,000	81	5	8-14
49	2,915	828,000	872,000	1,316,000	59	6	6-20
54	1,255	1,619,000	2,066,000	2,105,000		6	10-40

* Exposures were given daily at a distance of 16 inches (40 cm)

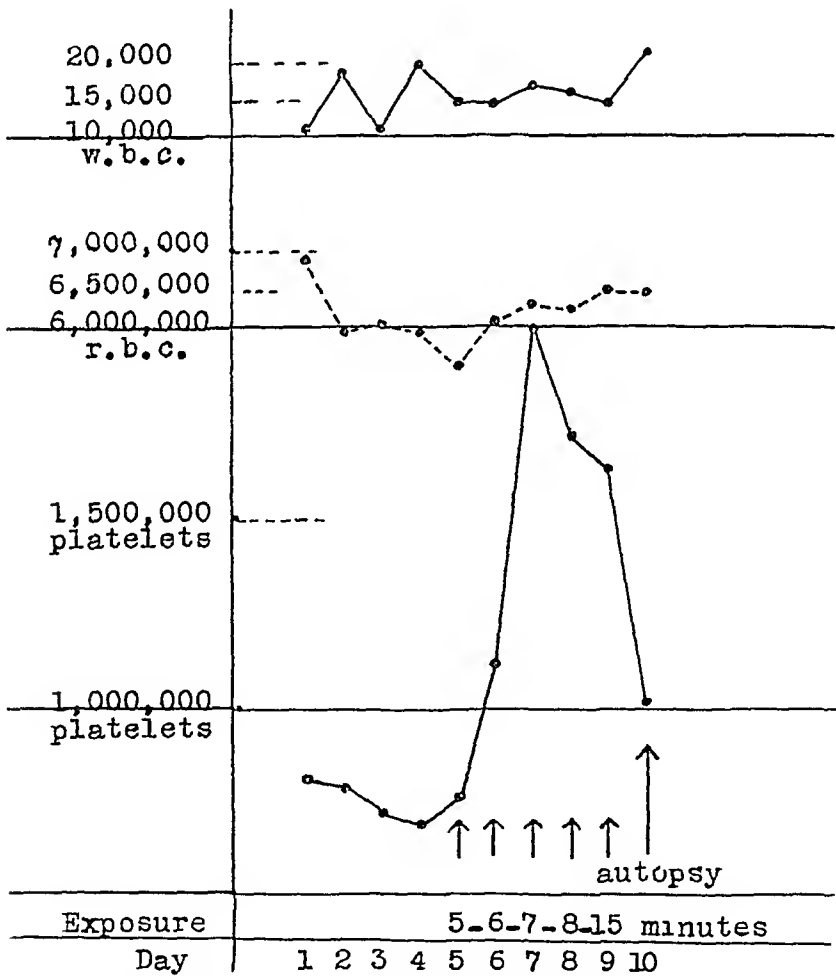


Chart 1—Effect of exposure to ultraviolet light on platelet, red cell and white cell counts of rabbit 46

first exposure R47 was refractory. After one attempt to increase the platelets, the rabbit was allowed to rest for two months, after which the hair was again clipped and the procedure repeated beginning with smaller doses of radiation, which were increased to massive doses, but no significant rise was seen. R54 showed an extremely variable platelet count throughout. It was consistently high (between 1,242,000 and 2,066,000 per cubic millimeter) before radiation, and, although more stable at a higher level after irradiation, it did not rise significantly. Autopsy revealed no pathologic condition grossly.

Comment—These results agree with those of previous investigators as to the general effects of ultraviolet light irradiation on the numbers of the blood elements, with special reference to that of the platelets. There is a rise in blood platelets following exposure to moderate doses, which begins in from one to three days, reaches a maximum within a few days, and then falls rapidly. There are rabbits, however, that do not respond to this type of stimulation. Also there are rabbits in which the daily fluctuation is normally very great. This makes it necessary to interpret all changes following experimental procedure with great caution. Furthermore, it seems that in susceptible rabbits changes can be produced with slight irritation, such as small lacerations of the skin. This must be carefully ruled out by making new normal counts after shaving or by clipping the hair instead of shaving.

EFFECT OF IODINE

The influence of iodine on blood platelets apparently has not been studied, as we have found no reference to it in the literature to the present time. Because of the wide application of iodine in surgery and its known irritating quality, a study of the effects of local applications of this drug on the blood elements seemed advisable.

Method—Six rabbits weighing from 980 to 1,710 Gm were used for this study. Tincture of iodine, U S P, was used. From one to five applications were made, at twenty-four hour intervals, to the skin of the back of each rabbit. The skin had been prepared previously by clipping the hair over areas varying in size from 7 by 10 cm to 8 by 13 cm. Two of the animals receiving more than one application were killed at the height of the increase in platelets. The blood elements of the other four were counted until the counts were normal.

Results—At the end of twenty-four hours, the iodine had practically disappeared from the skin. Thrombocytosis developed in four rabbits (see table 2 and chart 2) in from one to three days, which reached a maximum in a few days and then receded. In some cases, a secondary rise was observed. The return to normal was completed in about three weeks. The skin appeared normal for several days, after which erythema developed. It was not accompanied by any consistent leuko-

TABLE 2—Influence of Iodine * on Number of Blood Platelets

Rabbit	Weight, Gm	Platelets			Platelet Increase, per Cent	Procedure
		Normal Average	Normal Maximum	Experimental Maximum		
51	980	1,232,000	1,345,000	2,270,000	84	Back (8 by 10 cm) painted on three successive days
56	1,200	1,198,000	1,349,000	1,725,000	44	Back (8 by 10 cm) painted on five successive days
58	1,600	889,000	941,000	1,005,000	12	Back (8 by 13 cm) painted twice
62	1,280	834,000	911,000	1,642,000	97	Back (7 by 10 cm) painted once
64	1,710	869,000	1,107,000	1,256,000		Back (11 by 16 cm) painted once
65	1,520	848,000	1,092,000	1,027,000		Back (10 by 15 cm) painted once

* Tincture of iodine, U S P, used

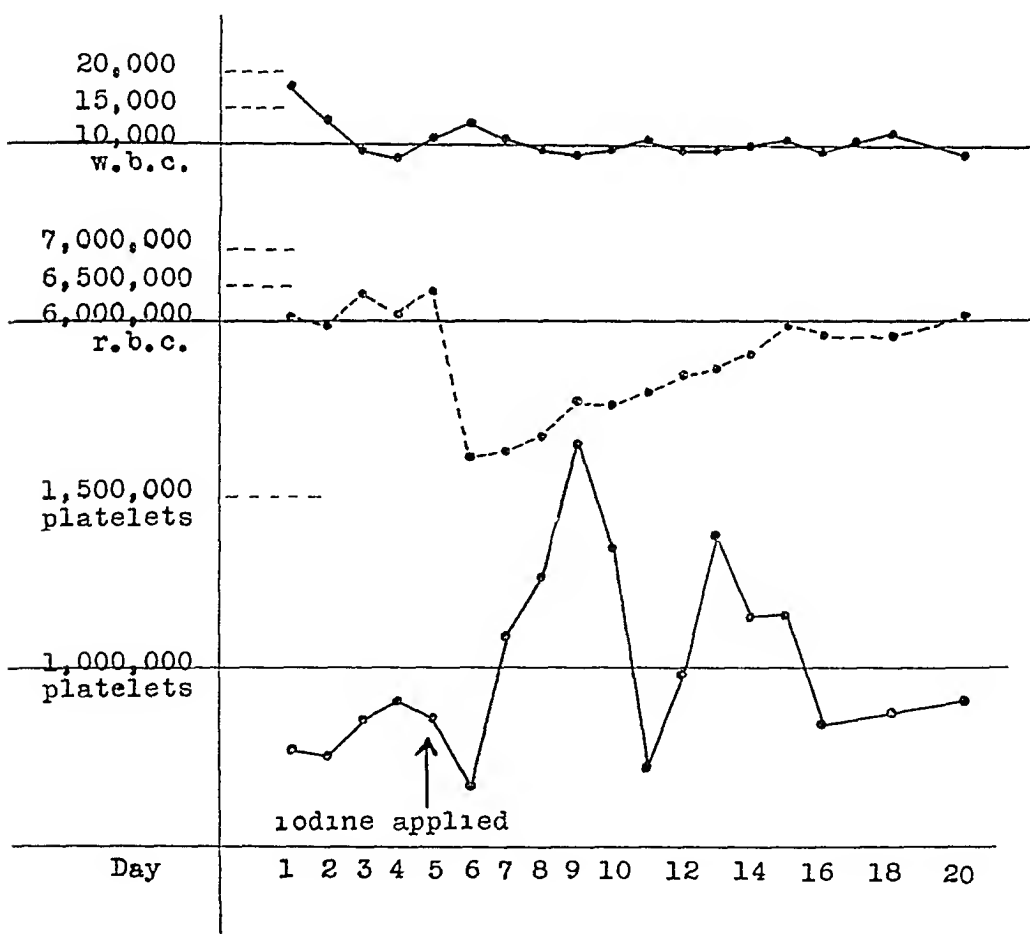


Chart 2—Effect of external application of iodine on platelet, red cell and white cell counts of rabbit 62

cytosis or change in temperature. The skin began to exfoliate in about two weeks. Hair grew into the new skin.

The leukocytes did not show any consistent change. Leukocytosis developed in R51 on the fourth day after three applications of iodine, but this animal was evidently sick and its temperature fell 2 F.

The erythrocytes showed a marked fall in twenty-four hours in two animals. There was then a gradual recovery completed in from two to three weeks. The other four animals showed little change in erythrocyte counts.

Comment—Thrombocytosis developed in four of six rabbits following application of iodine to the skin of the back. In two cases, marked anemia developed in twenty-four hours. At this time, thrombocytosis had not yet developed, so that there was an actual decrease in the number of platelets present. Thrombocytosis then developed quickly. Its significance is lessened, as it was not an isolated effect. It seems probable that the secondary thrombocytosis that sometimes developed was due to the low grade dermatitis. This was slow in healing and was probably the cause of the maintenance of the thrombocytosis.

EFFECT OF COAL TAR

The effect of local applications of coal tar on the formed elements of the blood has not been previously studied. It was used in these studies principally because of its prolonged irritating effect on the skin.

Method—Four rabbits were studied by the same method as that given for the study of the normal blood elements. Coke oven refined coal tar was applied to the skin of the back over areas from which the hair had previously been closely clipped, varying from 8 by 8 cm. to 8 by 10 cm. One application of the tar was made on each animal. All of the animals were studied until the counts of the blood elements were again normal.

Results—There was no consistent alteration of the leukocyte counts beyond the normal variation. The erythrocyte counts, also, were not affected (see table 3 and chart 3).

Thrombocytosis developed in two animals. This occurred on the third day in one animal and on the fifth day in the other. One of these rabbits then presented thrombopenia, which lasted about two weeks. Both of the other animals showed thrombopenia, beginning on the third and sixth days and persisting in both for about two weeks. These animals had anorexia for a few days after the applications of tar, but did not have a rise in temperature. There was a slight loss in weight. The tar dried in twenty-four hours and began to peel off in a week. The hair returned.

Comment—With the procedure used, coal tar had a variable effect on the number of blood platelets. It produced both thrombocytosis and

TABLE 3—*Influence of Coal Tar on Number of Blood Platelets*

Rab bit	Weight, Gm	Platelets					Platelet Change, per Cent	Procedure
		Normal Average	Normal Maximum	Experi- mental Maximum	Normal Minimum	Experi- mental Minimum		
59	1,070	338,000	1,090,000	1,496,000	698,000	513,000	+79	Tar applied once to area 8 by 8 cm
60	2,020	650,000	748,000	1,245,000	563,000	646,000	+80	Tar applied once to area 8 by 8 cm
61	1,750	1,143,000	1,233,000	1,209,000	1,001,000	686,000	-66	Tar applied twice to area 8 by 9 cm
63	2,445	626,000	733,000	796,000	450,000	401,000	-56	Tar applied once to area 10 by 10 cm

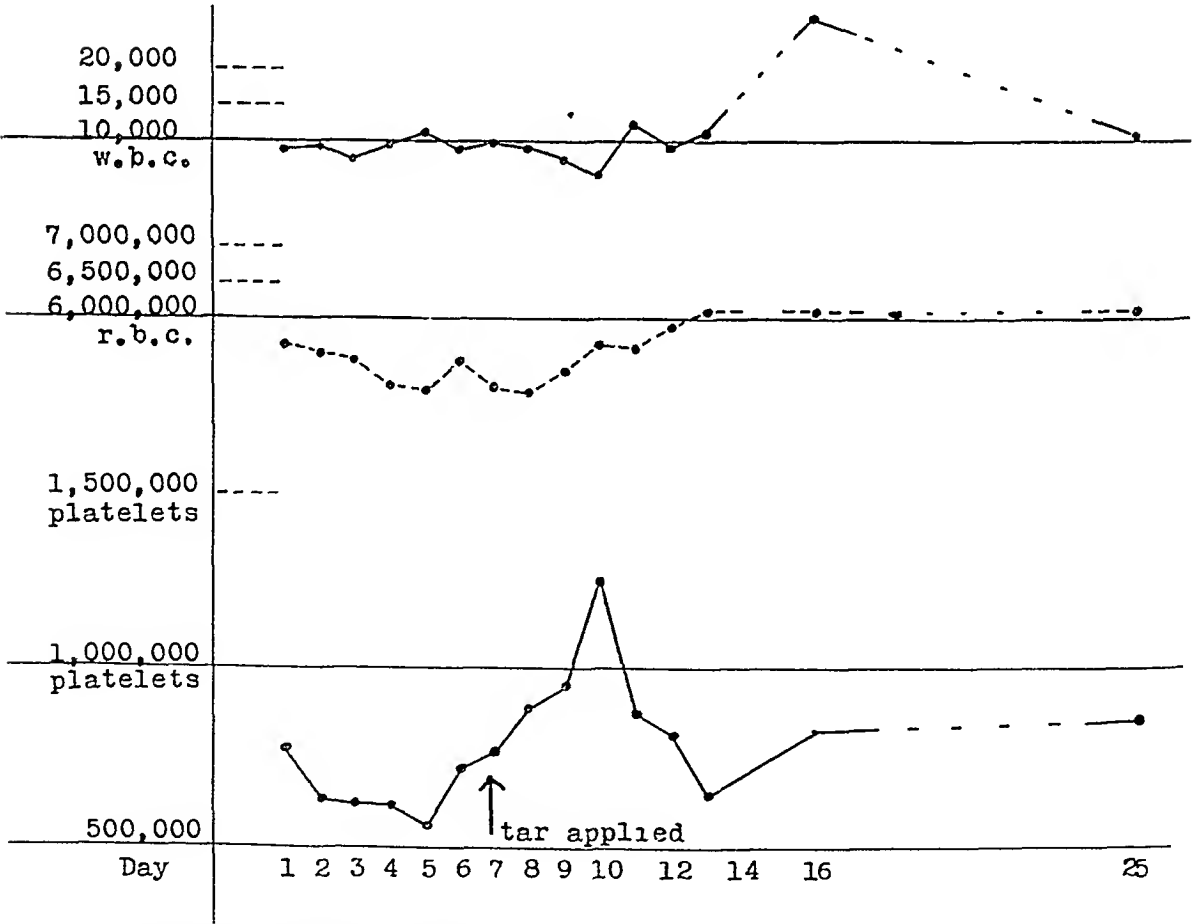


Chart 3—Effect of external application of coal tar on platelet, red cell and white cell counts of rabbit 60

thrombopenia This action is like that of benzene, bacterial toxins (Duke⁶) and many other toxic substances when the dose is varied Large doses, for this particular animal, lower, while smaller doses raise, the platelet level There was no perceptible effect on the other blood elements

GENERAL COMMENT

It has been shown that ultraviolet light has a rather specific effect in increasing the number of the blood platelets in the circulating blood The action has been ascribed by Vannfalt³³ to the release of some chemical substance in the skin which has the ability to excite the bone-marrow to produce thrombocytes

Iodine applied to the skin also increases the number of blood platelets in the circulating blood A secondary anemia is sometimes produced, so that the thrombocytosis is not an isolated effect The local effects of iodine are described by Sollmann³⁸

Elementary iodine precipitates proteins, the iodine being partly adsorbed, partly loosely bound, and partly converted into iodide ions This precipitation causes a persistent irritation, usually short of corrosion The action is chemical, since it precipitates proteins as easily dissociated compounds Elementary iodine is absorbed very effectively, but still only in very small quantity

Coal tar has a variable effect on the blood platelets, sometimes increasing and sometimes decreasing their number It is generally regarded as a skin irritant and produces a local erythema Little is known about its absorbability from the skin

The fact that all three of these agents cause local inflammation in the skin suggests that the common factor effecting alterations in platelet number might be some product of tissue injury This would coincide with the observations of those authors who observed thrombocytosis following various operative procedures³⁹

The mechanism of the changes in the blood platelets in these experiments is not clear Theoretically, the increases might be due either to stimulation of formation or to inhibition of destruction of the platelets A sudden release of stored platelets from the spleen into the blood stream also occurs, but Binet and Kaplan²¹ showed that such alterations are ordinarily of only about one hour's duration The altered form of the platelets during periods of rapid increase in number suggests that there is an increase in production Many other investigators have noted this morphologic change in experimentally produced thrombocytosis At

38 Sollmann, T. A Manual of Pharmacology, ed. 3 Philadelphia, W. B. Saunders Company, 1926, pp. 884-885 and 887

39 Bachman and Hultgren (footnote 17) Liles (footnote 18) Dawbarn, Erlam and Evans (footnote 19)

the beginning of the rise, small, dark-staining platelets appear, many of them with one or more slender, pointed processes. They become more and more numerous until, at about the time of the maximum rise, they constitute a large percentage of the total number of platelets. The normal round or ovoid, light-staining forms then gradually replace them. The small forms give the impression of being immature, recently formed platelets. Studies have been undertaken to correlate these variations with megakaryocyte activity.

An interesting phenomenon is that no matter what the stimulus consists of or how long it is applied there is a rather definite level above which platelets will not increase in number in the circulation, and no procedure so far used has been able to prolong this high level. The maximum increases have been from about two to two and one-half times the normal. Dawbarn and his co-workers¹⁹ have shown that the time relations of postoperative clinical thrombosis and embolism correspond exactly with those of the greatest platelet rise. This limitation phenomenon is possibly purposeful. As the origin and the fate of the blood platelets are not well understood, the mechanism in these conditions remains obscure.

SUMMARY

Ninety enumerations of the blood platelets, leukocytes and erythrocytes in the blood of fourteen normal rabbits were made. The average normal platelet counts in this group of animals were somewhat higher than those reported by other investigators.

The effect of ultraviolet light irradiation on blood platelets as reported by previous investigators was corroborated.

Iodine applied to the backs of rabbits caused thrombocytosis, beginning in from two to five days, reaching a maximum by the sixth day, and slowly receding to a normal level in from two to three weeks. Marked secondary anemia sometimes occurred within twenty-four hours, with a return of the erythrocytes to normal in from two to three weeks.

Coal tar applied to the back was followed by either thrombocytosis or thrombopenia. The numbers of the other blood elements were not appreciably changed.

The similarity between the effects on the platelet level of ultraviolet light and of other substances producing dermatitis suggests that the effects may be due to tissue injury and to the absorption of breakdown products that stimulate the formation of platelets.

THE SIGNIFICANCE OF INVASION OF BLOOD VESSELS IN ADENOMAS OF THE THYROID GLAND *

SHIELDS WARREN, M D

BOSTON

Although in cases of endemic goiter the adenoma-like nodules occurring in the thyroid gland cannot be differentiated from foci of abnormal involution, nevertheless certain of the more anaplastic, completely encapsulated masses may be considered as true tumors. A completely encapsulated mass found in a normal or a hyperplastic gland, and definitely varying in histologic appearance from the remainder of the thyroid gland in which it occurs, is in all probability neoplastic. The morphology of the adenomatous tissue varies widely as between individual tumors, but is fairly uniform as a rule throughout any given tumor mass. The thyroid material that I have studied, owing to geographic position, is not overrich in endemic goiter, so that the true adenomas can be fairly readily distinguished.

I have attempted to classify the adenomas into four groups according to the degree of differentiation which the adenomatous tissue shows. The papillary cystadenomas have been excluded from this study.

A growth that is made up of columns of small, closely packed cells with or without a considerable amount of stroma is considered an embryonal adenoma. This type shows little, if any, formation of alveoli, and colloid is almost never present.

The next group is slightly more differentiated. There are numerous small follicles of fetal type, often containing but a small amount or no colloid, and frequently sparsely sprinkled through an edematous stroma. This type of adenoma is peculiarly apt to undergo cystic degeneration or hemorrhage.

A third type, the simple adenoma, is made up of well differentiated thyroid tissue, often with a considerable amount of stroma, but definitely encapsulated and separated from the remainder of the gland, frequently its histologic appearance indicates a state of functional activity totally different from that of the bulk of the glandular tissue.

The fourth type, the colloid adenoma, is a completely encapsulated mass of thyroid follicles enormously distended with colloid and sharply varying in character from the remainder of the thyroid tissue.

* Submitted for publication, Aug 27, 1930.

* From the Pathological Laboratory, New England Deaconess Hospital, and the Lahey Clinic.

Owing to the frequency with which these adenomas occurred, it became necessary to determine whether they were as harmless as they appeared to be, and whether any criteria could be established for determining the presence or absence of malignant tendencies.

In gross, invasion of the capsule was considered a possible evidence of malignancy, but this proved unsatisfactory for microscopic diagnosis, except in advanced cases of malignancy. It was then hoped that invasion of the lumina of blood vessels by neoplastic tissue might present the criterion desired. The value of this method of determining the malignancy of thyroid tumors, first proposed by Graham,¹ has been well established by him and others, and in some instances it is the only definite histologic criterion.

Consequently, the group of adenomas received in this laboratory from the Lahey Clinic for the five years from 1923 to 1927 inclusive were studied with a view to classification of the adenomas and to the occurrence of invasion of blood vessels. During this period a total of 1114 adenomas was found, 34, or 3.1 per cent, showed invasion of

Adenomas of Thyroid Gland, 1923-1927

	Embryonal	Fetal	Simple	Colloid	Unclassified
Without invasion of blood vessels	62	477	270	247	15
With invasion of blood vessels	5	28	0	0	1
Total	67	505	270	247	16

blood vessels. The table shows the distribution of the adenomas by types.

The group of unclassified adenomas is made up of those varying so widely in histologic structure that they cannot be placed in any definite group, and also those that have undergone extensive cystic degeneration, leaving little or no clue as to the type of tissue previously present.

Of the thirty-four cases showing invasion of blood vessels, thirty-two have been followed for from two and one-half to seven years. The patients who are living and well number twenty-nine. One patient died of carcinoma of the uterus without any evidence of thyroid disease. All the cases showing invasion of blood vessels occurred in women, their ages ranging from 24 to 66 years.

Two patients, or 6.3 per cent, died with multiple metastases from the thyroid tumor.

The first case, DS25-930, occurred in a woman, 28 years of age, who had had an embryonal adenoma removed on June 20, 1925, because of difficulty in breathing. The nodule was completely encapsulated. No further treatment was given. In September, 1925, a small node was

1 Graham, A. Surg. Gynec. Obst. 42:781, 1924.

removed from near the scar of the previous incision. This also showed the structure of embryonal adenoma. In both these tumors a diagnosis of carcinoma could not be made either on gross or on microscopic structure, but several venules and capillaries showed definite invasion by the adenomatous tissue. The patient died on April 30, 1926, with multiple pulmonary metastases and a recurrence in the neck.

The second case, no. 38994, occurred in a woman, 29 years of age, who had had a fetal adenoma removed from the thyroid gland in 1924. In March, 1927, she reentered the hospital with a large mass in the throat and multiple pulmonary metastases. She died shortly afterward. On reexamination the adenoma showed invasion of blood vessels.

Of 1,080 surgically removed adenomas of the thyroid gland that did not show invasion of blood vessels, none has, so far as known, given evidence of thyroid malignancy for from two and one-half to seven years after operative removal.

On the other hand of thirty-four adenomas that showed invasion of blood vessels two occurred in patients who died from local recurrence and multiple metastases, one in ten months and one in two and one-half years. Since 1928 postoperative x-ray treatment has been given to all patients showing evidence of invasion of blood vessels. What effect this may have it is impossible to say, but it is of interest that no patient so treated has as yet presented either a recurrence or metastases.

Graham¹ pointed out the danger which adenomas of the thyroid gland present as possible sites of origin for carcinoma. This danger is accentuated by evidence of invasion of blood vessels. Seventeen of fifty-four cases of thyroid carcinoma reported by Clute and Smith² apparently arose from preexisting adenomas.

SUMMARY

Of 1,114 adenomas of the thyroid gland studied, 34 showed evidence of invasion of blood vessels. Of these 34, 2 occurred in patients who died from multiple metastases. In the fatal cases, the appearance was not any more suggestive of carcinoma than in the others. A guarded prognosis should be given in those cases of thyroid adenoma that show invasion of blood vessels.

¹ Clute, H. M., and Smith, L. W. Cancer of the Thyroid Gland, *Arch Surg* 18 1, 1929.

General Review

PULMONARY SYPHILIS

ITS FREQUENCY, PATHOLOGY AND ROENTGENOLOGIC
APPEARANCE *

MARY C McINTYRE, M D

KALAMAZOO, MICH

Before Virchow published a detailed description of white lung of the new-born infant in 1858, Pare, Astruc and Morgagni spoke of phtisie a lué vénérea Beyle (1810), Lagneau, Yvaren and MacCarthy (1844) attempted to draw attention to pulmonary syphilis, but their attempts failed. It was Virchow who centered attention on the subject of pulmonary syphilis, and his detailed description of the changes occurring in the lungs of the syphilitic new-born infant served as a basis for further research.

In a review of the cases of pulmonary syphilis reported between the years 1854 and 1906, sixty-five were found. Of these sixty-five cases seven were in new-born infants and fifty-eight in adults. The diagnosis of pulmonary syphilis was based on the result of antisyphilitic treatment in thirty-five cases, and in twenty-three cases the diagnosis was verified at autopsy.

The cases of syphilis of the lung in the new-born infant were reported by Lancereaux (1873), Cornil, Dubousquet-Laborde and Gauchiers, Duzeu, Fournier (1886) and Dieulafoy (1889, a). The cases of pulmonary syphilis based on the results of antisyphilitic treatment were published by Dufour, Landrieux, Lancereaux (1873), Fournier (1875, 1878), Poterlin du Motel, Cube, Lutz, Schech (1882), Engel, Gaudichier, Fournier (1886), Dieulafoy (1889, b), Panas, Feulard, Thompson, Julien, Levy, Zinn and Stengel. Those verified at autopsy were observed by Vidal de Cassis, Lancereaux (1873), Henop, Pawlinoff, Maigendorff, Councilman, Delepine and Sisley, Rolleston, Lancereaux (1892), Peterson, Storch, Salomon, Zinn, Nacke, Sheib, Galvagni, Cade and Jambon, Cade and Save, Clayton and Stengel.

In this same period (between 1854 and 1906) there were thirty-eight publications other than those mentioned that dealt with pulmonary

* Submitted for publication, Dec 26, 1930

syphilis These were written by Weber (1866), Moxon Hertz, Goodhart (1874), Grandicher, Greenfield (1876-1877), Goodhart (1877), Gowers, Green, Irvine Pye-Smith, Pittany, Randohn, Vierling, Schmitzler Paneritus Sokolowski, Hillel, Koeninger Porter, Potam (1885, 1888), Kidd Symonds Schech (1887), Ziemssen Mauriac (1888) Ruhemann MacDonald, Mauriac (1890), Perry, Satterthwaite, Hodenpyl, Marfan Abrams, Jacquinet, Boist Chretien Flockemann, Hansemann, Beig Dawson Conner Baumel, Hughes and Willson Sargent (1905) and Spitzer

In 1907 the diagnosis of pulmonary syphilis by means of the x-ray, was added to the diagnosis by therapeutic test and by the observations at autopsy Buchanan reported the first case in which treatment was controlled by x-ray photographs The literature between 1906 and 1920 yielded sixteen cases the diagnosis of which rested on the results of antisyphilitic treatment These were reported by Gullan, Millian, Grindon Roussel Brown Massia Colleville Burnham Covisa, Culver, Hoffman, Perret Landis and Lewis and Post

Between 1906 and 1920 twenty-five cases of pulmonary syphilis were verified at autopsy These were reported by Beriel Kokawa, Koch Osler Henske, Shingu, Brandenburg Sugar Bruhl and Lyon-Caen, Fowler Gerst and Weiss (cited by Massia) Massia Tanaka and Robertson

The twelve case reports published between 1906 and 1920 in which a diagnosis of pulmonary syphilis was based on x-ray evidence, were contributed by Buchanan, Massia, Blinder, Kavesi (1914), Bauch, Post, Lissner and Funk There were reports on two cases in which observations both by means of the x-rays and at autopsy were recorded These were given by Mosny, Malloizel (cited by Massia) and by Roubier and Bouget

Between 1906 and 1920 other papers appeared by Sargent (1908), Forsyth, Hansemann (1911), Downing, Easton, Hollman, Hays Kelty, Potter Williams, Wood, Casten and Denis, Boudet, Dexter, Leredde, Phipps, Tice, Warthin (1917), Watkins (1917), Witherspoon, Carman, Davidson and Callaway, Hall, Hoxie, Morris, Jr Rothschild, Schonfeld, Warthin (1918), Weber (1918), Groedel, Kayser (1919), Boislumene, Carrera, Watkins (1920) Karshner and Karshner and Adelberg

From 1920 to 1930 Bezançon and Jacob, Jacob, Letulle (1924), Howard, Letulle and Dalsace de Jong, Benda, Fiorentini, Gautenberg, Diest, Gaté, Dechaume and Gardere Gaté and Rousset, Koch (1929), Krohn, Vogelsang Windholz and Huguenin added reports of cases to the literature

INCIDENCE

Letulle said "In spite of its rarity white lung of the newborn has been described in detail and accepted while the existence of pulmonary syphilis in the adult, which according to some observers is not more rare, remains a debatable question" In 1905, Claytor found none in 13,000 specimens at the Army Medical Museum in Washington Stanley recorded 2 cases and a doubtful one in 1,000 autopsies The Copenhagen Hospital reported 2 in 6,000 cases, Peterson found 11 in 88 autopsies Stolper (cited by Karshner and Karshner) found syphilitic lesions in 86 cadavers, in 61 of which the lesions were due to acquired syphilis Of these 61 cases, 4 showed fibroid changes that were specific and 1 a gumma of the lung Osler saw 12 cases of pulmonary syphilis in 280 autopsies, and Carreira found that 8 per cent of 152 cases showed syphilis of the lung The Jefferson Chest Hospital (according to Karshner and Karshner) reported 4 cases in 1,200 autopsies, and Roque (according to the same authors) stated that syphilis of the lung was at least as frequent as syphilis of the liver

AGE AND SEX

Karshner and Karshner stated that the ages ranged from 2 to 98 years The average age was 36 years They found the disease commonest in the early thirties The disease affected males more than females in the ratio of 2 1, or seventy-six males to forty-two females The number of deaths due to the disease was greater in females (twenty-one deaths in forty-two cases) than in males (thirty-one deaths in seventy-six cases)

WHITE LUNG OF THE NEW-BORN INFANT

Since white lung of the new-born infant has been the basis for research in pulmonary syphilis of the adult, a description of it will be given

The macroscopic changes in pulmonary syphilis of the new-born infant depend on whether the lungs came from a fetus, from a new-born infant dying without having breathed or from an infant that has breathed In the fetus and in the new-born infant that has not breathed the lungs appear augmented in volume and are pale and of firm consistence They sink in water In the infant that has breathed the lungs show bleached islands that stand out vividly against the red color of the normal part of the lung The tissue is smooth, dry, nearly exsanguinated and decolorized The lymphatics are, as a rule, hypertrophied and fibrosed Microscopically there is a hyperplasia of fibrous tissue, accentuated in

the interlobular and interalveolar septums and in the peribronchial and perivascular tissues extending as far as the adjacent tissue beneath the pleura. All of the interstitial tissue of the lung is thickened owing to numerous fibroblasts with swollen protoplasm. These fibroblasts are fusiform in outline and have each a vividly colored nucleus that is often karyokinetic. A more or less exuberant production of elastic tissue accompanies these changes. In the midst of this connective tissue many capillaries, dilated and delimited by thickened endothelium, are seen. Plasma cells and lymphocytes are present. Around the vessels leukocytes collect in compact islands forming, at times, very small gummas (Dubousquet-Laborde and Gauchier, Duzeu, Fournier [1886], Dieulafoy [1889, a]). The centers of the islands may be occupied by masses of disintegrating material (Dieulafoy [1889, a], Dubousquet-Laborde and Gauchier, Lanceaux [1873]). In this caseated mass the bronchioles and vessels are obliterated. Several of the small gummas may coalesce to form a nodular gumma with polycyclic borders.

Some alveoli disappear, while others take the form of an acinus gland as the result of stricture and subsequent dilatation. These dilated alveoli are filled with epithelium, fat and macrophages. If the desquamated epithelium predominates in the dilated alveoli, the condition corresponds to the desquamative form of Virchow.

The change in the pulmonary vessels is usually more accentuated in the pneumonic zone surrounding the gumma and consists of perivascular hyperplasia. In the arteries the muscle cells and elastic tissue disappear and are replaced by fibrous tissue. An infiltration of leukocytes occurs here and there, and these groups may reach the size of a very small milium gumma. The lumen of the vessels is reduced, and they are lined by thickened endothelium. Obliteration may occur. Thrombo-arteritis is sometimes seen at the center of the caseating mass.

Spirochaeta pallida is always present. The spirochetes are, for the most part, in large mononuclear cells in the alveoli, but may also be seen in the bronchi, peribronchial fibrous tissue and in the epithelial protoplasm. All fibrous tissue, whether young or hyalinized, is infiltrated by them (Letulle, Virchow).

These changes in white lung of the new-born infant have formed the basis for the recognition of pulmonary syphilis in the adult.

CLASSIFICATION OF PULMONARY SYPHILIS

Karshner and Kaishner divided pulmonary syphilis into (1) pneumonic forms, (2) gummatous processes, (3) syphilitic pulmonary sclerosis, (4) bronchiectasis and (5) suppurative processes, ulceration and gangrene. Howard divided it somewhat differently into (1)

gummas, (2) chronic interstitial pneumonia, (3) pulmonary sclerosis, (4) syphilitic phthisis and (5) bronchopneumonia Krohn allowed but two forms (1) gumma, miliary and solitary, with or without cavity, and (2) the interstitial form, which may be accompanied by bronchiectasis Letulle gave a macroscopic classification of (1) solitary gumma, (2) massive fibrosis, (3) stellate scars and (4) islands of specific bronchopneumonia and a microscopic division of (1) "follicule elementaire" (the papule of early syphilis), (2) miliary gummas, (3) nodular gumma and (4) massive gummas

LOCATION

In the adult pulmonary syphilis usually affects one lung, the right one more frequently than the left The lower lobe of the right lung appears to be the site of predilection (Letulle) However, either lung or any region of either lung may be affected, even the apex, the place that earlier observers considered the site of predilection for tuberculosis Karshnei and Kaishnei stated that the disease begins more often in the upper lobes and spreads downward, and that at autopsy it is common to find active syphilis in the bases, with older fibrosed lesions in the right middle and upper lobes They concluded that pathologic changes in the right lower lobe strongly suggest syphilis In the Oxford Monograph (vol 5) there is a statement that a primary basal lesion is presumptive evidence against tuberculosis, and that syphilis is commonly found at the hilus and base In the cases that came to autopsy Lancereaux (1873), Mosny and Malloizel (Massia) Storch, Cade and Jambon, Duzea, Kokawa and Fiorentini found the right side involved, Henske, Beinel, Maigendoff, Massia and Tanaka, the left side The left apex and right base were found affected in the two cases reported by Goiest and Weiss (Massia) Both lungs were involved in the cases reported by Cade and Save (the exact locations were not given), Mosny and Malloizel (Massia), Roubier and Bouget, Henop, Shingu and Zinn In the group reported by Kaishnei and Karshnei the sites of the disease are given as follows the right lower lobe in 68 per cent, the right upper in 55 per cent, the right middle in 43 per cent, the left upper in 36 per cent, the left lower in 36 per cent and both sides in 36 per cent The cases diagnosed roentgenologically by Massia, Roubier and Bouget, Lisser and Funk were found to involve the right side Bauch and Post found the left side affected and Periet, Buchanan, Mosny and Malloizel (Massia), Blinder, Massia and Funk found both sides involved In all of these cases the sputum was negative for tubercle bacilli

PATHOLOGY OF PULMONARY SYPHILIS IN THE ADULT

In this review the form of pulmonary syphilis given under classification will be discussed without any attempt at reclassification. The first of these is the pneumonic form.

Hillel described a gelatinous form of infiltration corresponding to the catarrhal form of Beriel. The lobe is hard and contains no air. Its color is gray or red. On section it has a homogeneous gelatinous appearance, and on pressure a viscous fluid is obtained, which is rich in cells. There is an infiltration of the alveolar walls by small cells and the alveoli are filled with desquamated epithelium. The advanced stage shows an alveolar necrosis ending in fibrosis. Hillel believed that the infiltration was due to a compression of small pulmonary vessels by edema, or that it might be a combination of syphilitic pneumonia with ordinary pneumonia. Schnitzler thought it might be an early stage of indurative syphilitic pneumonia, but Beriel did not believe that it was specific.

In interstitial pneumonia due to syphilis the foci are well defined, fleshy and of elastic hardness. On pressure little fluid is obtained. Occasionally there are air bubbles and rarely crepitation. The lung sinks in water. Kaishnei and Kaishnei found that this type is often associated with bronchiectasis or with gumma. The connective tissue is more or less fibrosed, and microscopically the lung shows changes similar to those in white pneumonia of the new-born infant. The interstitial tissue is infiltrated by small cells, and the alveoli are smoothed out or collapsed. Other alveoli (Gaté and Rousset) are dilated and contain lymphocytes. Still others are newly formed. In places cells resembling epithelioid cells are seen. Giant cells with many nuclei, peripherally placed, may be seen, just as in tuberculosis. Small bronchi are infiltrated by lymphocytes and plasma cells. The adventitia of the vessels is thickened. Periarteritis is more common than endarteritis (Letulle). The pleura is infiltrated with the same cells and shows fibrosis of the vessels. Howard described chronic interstitial pneumonia as a diffuse infiltration in the middle lung. The lung is reddish yellow. It is smooth, airless and compact. The bronchi are sclerosed, and bronchiectasis may be associated with it. He stated that it is similar to a chronic, nonspecific pneumonia, but that it differs microscopically. Howard agreed with Warthin (1918), who stated that lymphocytes and plasma cells infiltrate blood vessels and lymphatics especially, and that there is a slight infiltration of tissue, with eventual fibrosis and atrophy or degeneration of the parenchyma. Warthin (1918) believed that the fibrosis may be directly due to syphilis, as well as to the chronic passive congestion which is present. Fiorentini stated that the fibrosis which

ensues in pulmonary syphilis cannot be differentiated from that of tuberculosis. Carrera found no pneumonic forms of pulmonary syphilis, but observed cases that responded to specific treatment.

Syphilitic bronchopneumonia was said by Letulle and Stokes to be infrequent, but Letulle stated that when islands of bronchopneumonia occur in a manifestly syphilitic lung they may be attributed to syphilis. Cavitation may occur as in tuberculosis. These islands are grayish white or grayish red and devoid of air. On section they are smooth and moist, cannot be penetrated by the finger, and show prolongations into the surrounding tissue. Some of these prolongations may reach the pleura, and at the point of contact the surface of the lung may be raised or serrated. All or almost all of the parenchymatous processes of the lung have been described as due to a bacillary caseous bronchopneumonia, but Letulle stated that syphilis may cause a process that is similar. The spirochete attacks the alveolar canals causing an exudation. The acute pneumonic focus due to the spirochete and its toxins affects alveoli, distends the interlobular acini and breaks down the interlobular septums and elastic tissue of the lung. In contrast with tuberculosis, the process almost always respects arteries and veins, but blocks the lymphatics. Caseous lymphangitis is one of the most striking traits of syphilitic bronchopneumonia (Letulle) owing to its size and volume. These islands may heal by the formation of scars or go on to cavitation. Occasionally the spirochete invades the scars causing them to break down as in tuberculosis.

If the process goes on to cavitation, the important bronchi in the caseous focus are ulcerated. Polymorphonuclear cells predominate, and fragments of elastic tissue may be seen. Even remnants of blood vessels and an isolated air space have been observed. *Spirochaeta pallida* can be demonstrated as a rule (Letulle). The cavity, when formed, shows three delimiting layers. The internal layer is jagged and friable. It is composed of granulation tissue and polymorphonuclear cells. In this layer may be found fragments of the organ, especially of blood vessels, which are recognized by the elastic tissue that is preserved in part and by the dead cells filling the lumen. Here and there elastic remnants of bronchi and alveoli may be found, if the tissue is stained especially for them. The second layer is a trilemma of connective tissue and condensed granulation tissue. This may arrest the process or be included in the zone of destruction. The third layer is composed almost entirely of plasma cells and lymphocytes. It represents the zone of centrifugal expansion in which spirochetes destroy the surrounding tissue. Here the borders of one island may meet those of another. These details recall the ulcerative process of tuberculosis, with the exception that blood vessels are not attacked.

As the spirochete invades the interstitial tissue of the lung, it may create the "follicule elementaire" described by Letulle. Mononuclear cells infiltrate the septums, and the entire alveolar wall is filled with plasma cells. They usually form a double line, the rows being regular, forming a delimiting membrane. This is said never to occur in tuberculosis (Letulle).

The lobule affected by an old, fibrosed, syphilitic bronchopneumonia appears to be encased by a thick and hyperplastic tissue. The subacute, then chronic, irritation causes this excess of elastic tissue to form. The hypertrophy and hyperplasia of the epithelium of the marginal alveoli may extend to the immediately adjacent lobules. Occasionally some of the alveoli directly in contact with affected lobules show cuboidal and hyperplastic epithelium, while other alveoli remain normal or become emphysematous. While the spirochetes destroy elastic tissue, they also excite its growth, causing the excess seen in chronic cases.

The pulmonary veins in the region affected are not invaded as in tuberculosis. The latter causes a panphlebitis or thrombosis, while syphilis causes periaarteritis or panarteritis (Windholz), with or without thrombosis. Infrequently the veins are attacked in a circumscribed area of the subendothelium. The mesothelium does not participate to any great extent, and the endothelium is intact. The adventitia is the site of attack. This is a point of differentiation between tuberculosis and syphilis of the lung.

The presence of a gumma may be suspected when an indurated mass is felt more or less near the pleural surface (Letulle). Karshnei and Kaishnei found it in 50 per cent of their cases. Warthin (1918) stated

The gumma is not the essentially typical lesion of old or latent syphilis. It is a relatively rare formation. The essential tissue lesion of either late or latent syphilis is an irritative or inflammatory process, usually mild in degree, characterized by lymphocytic and plasma cell infiltration in the stroma, particularly about the blood vessels and lymphatics, slight tissue proliferations, eventually fibrosis, and atrophy or degeneration of the parenchyma. These mild inflammatory reactions are due to the localization in the tissues of relatively avirulent spirochetes. The pathologic diagnosis of syphilis is essentially microscopic.

On section the gumma is seen as an opaque mass with a fibrous capsule. The color varies with its age, being rose-white, whitish gray or dull yellow. It may be round or polycyclic, depending on whether it is a solitary gumma or a number of gummas that have coalesced. Its diameter varies from a few millimeters to 1 cm or more. The consistency of a gumma depends on its age. A young, solitary gumma may be grayish red, translucent, firm and of uniform consistence. The fibrous capsule is compact and shiny and shows no anthracotic deposit.

An older gumma shows necrosis in the center and at a still more advanced stage a white, shiny, retractile, stellate scar which shows no anthracosis

In the evolution of a gumma Letulle described four stages (1) "follicule elementaire," (2) miliary gummas, (3) nodular gumma and (4) massive gumma

The "follicule elementaire" is characteristic of the early stage of pulmonary syphilis and consists of spirochetes and lymphocytes. It is round, is located in the interstitial tissue and has a predilection for small bronchioles, blood vessels and interlobular and interalveolar septums. Giant cells are rarely seen, and plasma cells predominate. The venules and bronchioles appear to be immobilized by the cellular infiltration. Frequently the arterioles, venules and bronchioles in the segment in contact with the "follicule elementaire" may be infiltrated (positive chemotaxis)

The second stage in the evolution of a gumma is the formation of miliary gummas. These are spherical, contain spirochetes and vary in size. The very young miliary gumma contains leukocytes, plasma cells and lymphocytes. Often these cells are more at the periphery than at the center and in this position appear to oppose the extension of the spirochetes. In the center and at the periphery many blood vessels of varying size are seen the lumina of which are large and filled with leukocytes and erythrocytes. Lymphatic vessels are filled with leukocytes. Giant cells are rarely seen, but plasma cells and capillaries are numerous. The area of inflammation containing spirochetes is rich in collagenous fibers. The walls of the blood vessels present and newly formed are thickened. Subpleural bands may extend from the hilus to the periphery causing depressions and forming lobulations.

The gumma may heal, leaving a scar with polycyclic borders if several gummas have coalesced, and hyaline degeneration or caseation may occur.

The central part of a caseous gumma contains granulation tissue and leukocytes undergoing karyorrhexis, and the peripheral part, fibrosis. The three zones of a gumma described by Carnei will be given later. The adjacent tissue participates in the process.

The surrounding tissue is poorly circumscribed, and beyond the lymphocytic zone are islands in which the alveoli are filled with plasma cells and lymphocytes and are edematous. Hemorrhage is rare. In places near the lymphocytic zone the interlobular and interalveolar septums are thickened, as well as the lining of the alveoli. Desquamated material fills the alveolar lumen. Around the venules and arterioles, beneath the pleura and between alveoli are lymphocytes and plasma

cells. The area of inflammation tumefies, an exudate forms, leukocytes migrate, and cells, blood vessels and lymphatics become hyperplastic. Centrifugal compression results. The alveoli and alveolar canals are compressed. The blood vessels and interlobular septums bend about the mass even to the point of distortion.

The progressive and centrifugal expansion of miliary gummas form the nodular gumma. A nodule may be found in the middle of a lobe characterized by necrosis similar to that described for miliary gummas, but it is larger and has more irregular boundaries. The nodule may be circumscribed by dense fibrous tissue, rich in plasma cells and lymphocytes, which form the zone of expansion. The same combative elements are seen in the nodular gumma that are seen in miliary gummas.

Carrera described three zones about a gumma: a central caseous area, an intermediate fibrous zone with many new blood vessels and an outer vascular, infiltrated zone rich in plasma cells and lymphocytes.

The central caseous zone presents the appearance of coarsely granular caseation in which few nuclei in varying stages of karyorrhexis are seen. The outlines of capillaries containing blood cells and fibrin can still be made out. There is no fibrin present in the caseous area except in these vessels, in contrast to the fibrin threads so abundantly found in the caseous centers of the tubercle. The intermediate zone is made up either of young fibrous tissue or of an older, more hyaline form but never distinctly epithelioid as in the tubercle. Fibroblasts appear and great numbers of angioblasts in the form of cords or young capillaries containing blood cells. The zone usually shows many plasma cells and lymphocytes and these increase in number in the outer zone, which may appear to be composed almost entirely of plasma cells, but capillary proliferation and increase of stroma can always be determined in this zone. The larger blood vessels in part show syphilitic endarteritis, particularly when the vessels appear to be the starting place of the gummatous process. Other vessels show hyaline degeneration. Many small infiltrations of lymphocytes and plasma cells with occasional endothelioid cells occur.

According to Letalle the perigummatous pneumonia is no less specific than the gumma. New connective tissue and blood vessels are found, and bronchioles are destroyed and replaced by granulation tissue, which is thin and uniform. Only the arterioles and venules escape. The process in the surrounding areas may affect entire lobules. It is usually dotted with elementary follicles. At the onset and during the evolution of a gumma this area is moist, is rich in new blood vessels and has many fibroblasts and much collagen. After an indefinite period scar tissue forms, which is poor in blood vessels and frequently undergoes hyaline degeneration. The alveoli that have escaped are thickened, sinuous and enlarged, but are incapable of more than their normal amount of work.

Massive gummas differ from nodular gumma only in the size of the caseated area. When healed, their borders are polycyclic and send prolongations to the pleura.

Massive fibrosis, according to Letulle, is less rare than solitary gumma of the lung. It is found in the interior of the lung as coalesced islands enclosed in large cirrhotic plaques. A fine network is seen throughout the parenchyma of the lung. The connective tissue following bronchi, blood vessels and interlobular septums is thickened, radiations from the hilus are seen, and induration of the surface of the pleura by bands of fibrous tissue cause lobulations and furrowing analogous to that seen in hepatic syphilis.

Carrera stated that a positive diagnosis of syphilis cannot be made in such cases without the typical inflammatory process due to the local action of the spirochetes, of which fibrosis is the sequel. It must be diagnosed from active areas, though certain aspects of the scar may be of aid. In a study of 152 affected lungs of syphilitic persons and 60 of persons with pulmonary tuberculosis he was unable to distinguish the fibrosis of syphilis from that of tuberculosis.

Bronchiectatic cavities were reported by Cade and Jambon, Cade and Save, Roubier and Bouget, Beriel, Brandenburg, Lancereaux (1873), Massia, Tanaka and Fowler. These bronchiectatic areas may simulate cavities. Carrera found no case of bronchiectasis, but found two cases of syphilitic peribronchitis, the essential changes in which were infiltration by plasma cells and the formation of new blood vessels. The vessels showed the typical infiltration of the intima and adventitia by plasma cells and lymphocytes. Newly formed muscle cells in connection with the bronchi were observed by him. The elastic tissue was either destroyed or displaced by the infiltration. Diest described panbronchitis in medium-sized and small bronchi resembling chronic bronchitis with bronchiectasis. Gate, Dechaume and Gardère also found bronchiectatic cavities in their cases.

Karshner and Karshner found that pus could be squeezed from the air spaces and bronchi in lungs showing chronic bronchitis. This condition was found in 13 per cent of the cases studied. There is a dense infiltration by small cells, which, they stated, should not be confounded with milium gummas, the latter being very dry in comparison.

Howard stated that the term syphilitic phthisis is an old one designed to include pneumonic forms, gummas, cavitation, bronchiectasis and fibrosis. Karshner and Karshner stated that a gumma may develop near the wall of a bronchus, ulcerate and empty into it, forming a cavity.

The gangrenous forms of pulmonary syphilis have not been well established. Kaishnei and Karshner expressed the belief that they represent a secondary infection in an ulcerated gumma or the end-result of endarteritis.

The scars of syphilis are radiating, stellate and, as far as one can judge, the remains of foci of resorbed or obliterated caseous gumma. These may occur anywhere, but more often at the base than at the apex. They are pearly white and thin. Their contiguity to injured bronchi or blood vessels, their configuration and the absence of lesions (Letulle) favor the diagnosis of an infection that acted with great intensity, had multiple foci and terminated by healing that was most destructive. In regions where parasitic infections (*Echinococcus*) are rare, tuberculosis and syphilis are the only diseases known that can produce such changes. Tuberculosis is not apt to produce such long fibrous scars centered about a resorbed caseous focus without anthracosis.

When syphilis attacks the bronchi, the spirochetes can be found in an area up to and including the epithelium, the protoplasm of which is the site of predilection for the organism. The inflammatory reaction excited may be acute, subacute or chronic and may be on the inner surface of the canal or in the bronchial wall. The process may be circumscribed and isolated, just as in an artery. It may confine itself to a segment of the bronchus, reducing that portion to a small ring. The process varies in intensity. At first hyperdiapedesis and simple hyperplasia are seen. It may be confined to the epithelium, and the infiltration by plasma cells and lymphocytes may affect only the internal surface of the canal, producing a simple catarrhal inflammation with hyperplasia and desquamation. This process is essentially benign and transitory. The same process propagated along the terminal passages as far as the alveoli would cause a broncho-alveolar catarrh comparable with white lung of the new-born infant.

The ulcerative reactions in the bronchial walls are more intense and destructive. The epithelium proliferates, desquamates and almost disappears. Granulation tissue forms at the expense of the lining of the bronchi. Elastic tissue is fragmented and atrophied over large areas, and an annular band of connective tissue forms, which is rich in newly formed vessels and infiltrated by a variety of cells in which plasma cells and lymphocytes predominate. Suppuration is not extensive. On the contrary, organization of fibrous tissue takes place quickly. This organized fibrous tissue extends for some distance, encroaches on adjacent alveoli and causes mutilation of the tissue. At the periphery of this fibrous tissue the zone of invasion and centrifugal expansion is seen, and here islands of syphilitic pneumonia may occur.

Bronchi deprived, in large or small part, of their elastic tissue are said (Letulle) to be not infrequent, if a careful study is made of all cases of proved syphilis that come to autopsy. The presence of aneurysm-like segments of a bronchus should be considered as well as of those in an artery. These dilatations may follow one another in a series. These and bronchiectatic cavities should receive careful study before syphilis is ruled out. It is not inferred that any or all annular dilatations are syphilitic, but that syphilis should be borne in mind.

The ulceration may spare a few islands of tissue, 1 mm. or more in size, although the rest of the bronchial wall is seriously involved. The larger arteries are usually left intact, although the pulmonary artery has been seen to be affected (Warthin, 1917). Endarteritis and periarteritis serve to confirm the diagnosis of syphilis in certain destructive conditions of the lung. Warthin (1918) stated that the pulmonary artery is affected in the same way as the aorta.

The inflammation may go on to a chronic state. Islands of chronic bronchitis, fibrosed and atrophied, may be all that remains as a proof of the existence of syphilis.

The pleura is frequently involved in syphilitic processes of the lung (Fiorentini, Letulle). On section of a manifestly syphilitic lung, one can, with careful search, demonstrate "follicule elementaire" (Letulle) as characteristic as those in the subjacent pulmonary tissue. The serosa is filled with mononuclear cells arranged in an irregular manner along the interstices. In places one may find groups of these "follicles," and spirochetes may be demonstrated in them. Plasma cells and lymphocytes are found around blood vessels and lymphatics. The meshwork of fibrils is filled with desquamated epithelium, leukocytes and erythrocytes. The presence of spirochetes in pleural effusion has not been demonstrated satisfactorily (Letulle), but the tubercle bacillus has not always been demonstrated in effusions believed to be tuberculous.

Syphilis causes a production of new connective tissue in the pleura that is even greater than that produced by tuberculosis. This causes a thickening of the pleura. New blood vessels are seen filled with mononuclear cells. Letulle stated that caseous material has been seen to pass into the pleural space.

The scar formed in the pleura is no less characteristic than that which develops in the subjacent pulmonary tissue. In breaking down, the lung will carry some segments of the serosa deep into the parenchyma, and the subjacent lobules may become bronchiectatic. The cortical pulmonary lesions adjacent to the pleura are greater in number in pulmonary syphilis than in pulmonary tuberculosis (Letulle).

In discussing the differential diagnosis, Cariera said

The formed gumma and the developed tubercle can be distinguished by the vascular, more closely packed epithelioid, sharply circumscribed, conglomerating character of the latter while the gumma appears as a more loosely arranged, less sharply limited, vascular granulation tissue, scant in epithelioid and giant cells and infiltrated with lymphocytes and plasma cells. The scar of the tubercle is round, sharply delimited with concentric fibers, hyalin, scant in nuclei, devoid of vessels and elastic tissue, less given to anthracotic pigment but more frequently calcified and very often confluent and conglomerated. The scar of syphilis is irregularly radiating or stellate, not sharply delimited, more like ordinary cicatricial tissue, still contains blood vessels, often with angiectatic capillaries, continuous with the thickened walls of the nearest alveoli, still shows elastic fibers and the outlines of old vessels and alveolar walls, the scars of gummas are extremely rarely conglomerated or confluent, the syphilitic fibrosis begins under the pleura and around the bronchi and is more frequently anthracosed and very rarely calcified. But the most conclusive differential point is the finding in the fibrosis of syphilis of collections of plasma cells, and such active areas are probably as frequent in syphilitic fibrosis of the lung as they are in syphilitic processes elsewhere in the body.

Karshnei and Kaishnei stated

Differentiation at the autopsy table of a gumma of the lung from similar tuberculous lesions is difficult. In favor of gumma are: 1 Location. Tuberculous nodules most commonly occur in the parenchyma. 2 Absence of calcification. Calcification is unknown in gummata of the lung. On the other hand, fatty degeneration is said to be more common in gumma. 3 Encapsulation. This is said to be a constant finding in gummata of the lung, it is more rare in tuberculosis. Microscopically the following are said to aid in diagnosis: 1 In gummata the fundamental structure of the normal tissue is said to be recognizable. 2 The presence of more or less altered blood vessels is characteristic of gumma. 3 Newly formed alveoli with cubical epithelium is mentioned more frequently in gumma than in tuberculosis. 4 Endarteritis obliterans and peri-arteritis are more common in gumma than in tuberculosis. 5 Infiltration of the small bronchi occurs more frequently in syphilis. 6 Proliferation of smooth muscle fibers is characteristic but not constant of gumma.

Koch (1929) stated that when calcification does occur in pulmonary syphilis, it is only in the gummatous form, and Gaté, Dechaume and Gardeie described a case of calcified gumma. Windholz described the characteristics of pulmonary syphilis as the presence of fibroblasts at the periphery of the granulation tissue, lymphocytes, plasma cells, and obliterative bronchitis and peribronchitis. In contrast with tuberculosis in which the caseation is of an exudative type, syphilis shows a productive reaction.

From the data contained in this paper the following points may be summarized: 1 The caseating power of syphilis is more limited than that of tuberculosis. 2 Healed tuberculosis is circumscribed, while the lesions of syphilis show prolongations. 3 Giant cells are rarer in

syphilis than in tuberculosis 4 Plasma cells are rare in tuberculosis than in syphilis 5 Anthracosis is more infrequent in the scar of syphilis than in the scar of tuberculosis Canera believed the opposite to be true 6 The nodule of tuberculosis may arise without a "follicule elementaire," and may begin as an island of encapsulated broncho-pneumonia 7 The invasion of a scar with subsequent breaking down is less common in syphilis than in tuberculosis 8 Blood vessels are more rarely attacked in syphilis 9 The adventitia of the blood vessels is the portion that is more frequently affected in syphilis 10 There is no epithelioid formation in syphilis as in tuberculosis 11 The elastic tissue is better preserved in syphilitic than in tuberculous processes 12 Syphilis produces a greater amount of connective tissue in the pleura than tuberculosis 13 Tuberculosis does not show as many cortical pulmonary lesions adjacent to the affected pleura as syphilis

ROENTGENOLOGIC DIAGNOSIS OF PULMONARY SYPHILIS

In 1907, Buchanan published a case of a man who, for one year, had had a condition diagnosed as tuberculosis, but in whose sputum tubercle bacilli could not be demonstrated. An x-ray film showed areas of infiltration in the bases of both lungs. These cleared up under antisyphilitic treatment. In 1910, Massia published three cases in two of which treatment was given followed by clearing up of the shadows on the film. One came to autopsy. In the latter case the x-ray photograph showed the apexes of both lungs to be involved, and at autopsy a diagnosis of white pneumonia was made, and the upper right bronchus was found to be filled with pus. Massia could demonstrate no spirochetes in the tissue. Roubier and Bouget, in 1912, reported one case in which the x-rays showed marked involvement, and at autopsy a syphilitic pneumonia was found on the right side with newly formed alveoli. In 1914, Kayser reported a case in which the shadows in the x-ray pictures cleared under antisyphilitic treatment. Two years later, Bauch reported dense fibrous bands over the entire right lung, with cavities that were probably bronchiectatic. In the same year, Lisse reported marked involvement of the cardiohepatic angle which cleared with treatment. In 1919 and 1920, Funk reported three cases. The first showed peribronchial thickening in the right lower lobe, which cleared up under antisyphilitic treatment. The second showed bilateral involvement, which cleared. The third showed an infiltration of the lower border of the upper right lobe and the upper border of the right middle lobe. In the lower lobe there was a great deal of fibrosis with possibly a bronchiectatic cavity. Others who have reported cases are Blinder, Post, Warthin (1917), Watkins (1917), Fiorentini Diest, Krohn and Gaté and Rousset.

The x-rays establish a point of contact between the clinical observations and the results at autopsy. It may be possible to state from observation of a film where the site of the lesion is, but it is not possible to diagnose the cause definitely.

The shadows seen in an x-ray film may be due to fibrosis sufficient to arrest the rays. This fibrosis may be in the bronchi, blood vessels or interstitial tissue. Of the three sites, the bronchial is the most common.

When cardiovascular syphilis already exists and questionable shadows are seen by means of the x-rays, the question arises. Do these shadows represent bronchial fibrosis or fibrosis of the pulmonary artery? In the latter event another question presents itself. Are these shadows due to syphilis of the blood vessels, since it has been stated that syphilis respects the integrity of these structures (Letulle)? It has been stated (Letulle) that when cardiac syphilis exists, primary syphilis of the lung is ruled out as a cause for the shadows seen.

In cases of proved pulmonary syphilis, fibrosis, which has a predilection for the bronchi, if present in the pulmonary tissue, shows, in the x-ray pictures, fibrous tracts more or less seriated. These tracts radiate from the point where the main lesion is located. Large cicatricial tracts cast polycyclic shadows. The arborescent tracts are fanlike (Diest, Fiorentini, Kiohn) and can be traced to their ultimate ramifications. Between these tracts are shadows due to perilobular and interlobular fibrosis. Fiorentini stated that roentgenologically the fibrosis in syphilis cannot be distinguished from that in tuberculosis, but that sclerosis localized at the hilus, calcification or cavity points to tuberculosis, and that peribronchial sclerosis with formation of rings points to syphilis.

The parenchymal shadows remain more or less circumscribed and are secondary to the sharply defined arborescent tracts. Enlargement of the mediastinal nodes or calcified nodes and annular shadows may be seen just below the hilus. These rings are probably due to fibrosis around bronchi (Fiorentini) and that portion of the bronchial tree near the median line and may occur in groups of three or four. Following the oblique direction of bronchi one may find black half circles or a more or less elliptical shadow devoid of lumen.

Arborescent tracts, diffuse fibrosis radiating in all directions from and along bronchi even to their termination, more or less marked emphysema and an enlargement about the hilus are some of the aspects of pulmonary syphilis. Even when other diseases are operating in the lung, one should not fail to look for these signs. It is not impossible that a second disease may be acting in a field already affected by syphilis.

In those cases of fibrosis in a dihybrid terram there is frequently an extreme production of fibrous tracts (Gaté and Rousset). In some

cases calcified nodules or enlarged nodes may be seen extending from the mediastinum to the cervical region in an uninterrupted chain (Letulle)

When the exuberant fibrous tracts join apical shadows, causing a more or less homogeneous opacity, one should consider that a fibrous tuberculosis is grafted on a syphilitic terrain and look for parahilar shadows and calcified nodules. Tuberculosis may attack the bronchi, but the shadows will be finer and the annular rings less dense than in syphilis.

Watkins (1917) stated that pulmonary syphilis must be differentiated from bronchiectasis, abscess, malignant growth, pneumoconiosis, unresolved pneumonia and tuberculosis.

Shadows due to carcinoma will give sharp margins, while syphilis has irregular borders. Watkins (1917) believed that the absence of cavity is peculiar to syphilis, but Massia, Beigel, Stoich, Cade and Jambon and Fowler reported cavity in pulmonary syphilis.

Pneumoconiosis, according to Watkins (1917), resembles syphilis and tuberculosis combined. He also stated that no roentgenologic differentiation can be made between pulmonary syphilis and unresolved pneumonia.

As a rule, the shadows due to syphilis are in the lower and middle lobes, while those due to tuberculosis are in the upper lobes. The densest shadow in syphilis begins at the hilus and diminishes toward the periphery, while in tuberculosis the characteristic shadows are about the apical and subapical regions.

No definite points of differentiation of pulmonary syphilis from other pulmonary conditions can be given, with the exception possibly of the radiating fanlike lines seen in x-ray films, and the location, which is usually the lower lobes, more especially that on the right side.

The demonstration of spirochetes in the sputum or tissue establishes the diagnosis. While it is a routine procedure to search for tubercle bacilli, it is only in the exceptional case that spirochetes are looked for. In 1907, Koch found them in a case that came to autopsy, in 1908 Henske stated that the lung he examined was densely filled with them, in 1910, Massia reported that he had searched for them but had not found them, and in 1917, Warthin reported a case of syphilitic aneurysm of the pulmonary artery and with it the demonstration of spirochetes. In 1929, both Vogelsang and Windholz reported the presence of spirochetes.

Warthin's critical morphologic studies of syphilis and Wile's dictum that spirochetes should be searched for until found might well be applied to future research in pulmonary syphilis.

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Notes and News

Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation—During the seventh year of this foundation 25 grants were made, 21 to scientists in other countries than the United States. Seventy-eight applications were received, 62 from foreign countries. In the seven years of its existence, the foundation has made 120 grants. In accord with the policy of aiding work on similar or related problems, investigations bearing on the general subject of nephritis have been given preference, the same is true also, but to a less extent, of work on internal secretion and infection. Applications should state the nature of the research proposed, the amount of money wanted, and the objects for which the money is to be used. Applications for grants should be sent to the secretary, Joseph C. Aub, 695 Huntington Avenue, Boston, before May 1, 1931. Walter B. Cannon is the chairman of the executive committee.

Regulation of Blood Donors in the City of New York—In March, 1928, under the leadership of the committee on blood groups of the National Research Council, an experimental bureau was established in New York City, the main purpose of which was to supply the hospitals and private physicians in the city with properly examined blood donors.

An important secondary object was to acquire a practical experience with such a service from which could be drawn up needed regulations for the control of blood donors and donor agencies by the Board of Health.

About two years after it was started, this bureau was taken over by the Blood Transfusion Betterment Association which had been incorporated for the purpose under the auspices of the New York Academy of Medicine.

With this authority behind it, the bureau has been able greatly to extend its service without increasing its professional staff. Fifty hospitals are being served and approximately 300 donors are supplied each month.

The trustees of the Association have approved the policy of encouraging research in the bureau on all problems relating to transfusion of blood and knowledge of the blood groups.

The regulations formulated for the registration of all blood donors and for the control of donor agencies by the New York Department of Health are given in the following new sections recently added to the Sanitary Code by the Board of Health.

Section 108 Blood donors regulated, registration required, blood donor defined. No person shall act as a blood donor in the City of New York without a certificate of registration issued by the Department of Health or otherwise than in accordance with the regulations of the Board of Health.

"Blood donor" defined. The term "blood donor" as used herein shall be taken to mean and include any person who holds himself out as willing to dispose of his blood, or who offers his blood, or whose blood is used for transfusion purposes, for a fee.

Section 109 Blood donor agency. No person shall conduct, maintain or operate a blood donor agency in the City of New York without a permit therefor issued by the Board of Health or otherwise than in accordance with the terms of the said permit and the regulations of the said Board.

"Blood donor agency" defined. As used herein the term "blood donor agency" shall be taken to mean and include any office, registry, place or establishment which employs, engages or supplies or advertises or holds out to employ, engage, or supply any person or persons whose blood is or may be used for transfusion purposes.

Abstracts from Current Literature*

Experimental Pathology and Pathologic Physiology

THE INFLUENCE OF THE PERICARDIUM ON ACUTE CARDIAC DILATATION PRODUCED BY VAGAL STIMULATION E J VAN LIERE and G CRISLER, *Am J Physiol* **94** 162, 1930

Further evidence of the protective action of the pericardium in conditions of extreme cardiac stress was furnished by the fact that incision of the pericardium permitted greater cardiac dilatation following vagus stimulation than occurred in that circumstance in normal animals

H E EGGERS

THE EFFECT OF INSULIN ON GASTRIC SECRETION P F MAYER, *Klin Wchnschr* **9** 1578, 1930

Insulin in the chylic stomach increases the acidity and usually the volume of gastric secretion from seventy to ninety minutes after injection. The effect of insulin on the gastric secretion is an early symptom or a coincident manifestation of hypoglycemia, because the curve of the blood sugar is the inverse of that of the gastric secretion. Diabetic persons have no gastric reaction unless they become hypoglycemic. Their gastric reaction when hypoglycemic is the same, but less intense, than that of healthy persons

AUTHOR'S SUMMARY

THE PRODUCTION OF OSTEITIS FIBROSA BY PARATHYROID EXTRACT H L JAFFE, A BODANSKY and J E BLAIR, *Klin Wchnschr* **9** 1717, 1930

The subcutaneous injection of parathyroid extract into guinea-pigs regularly produced the bone changes of osteitis fibrosa. Similar results were noted in dogs, although the changes were produced with greater difficulty

EDWIN F HIRSCH

EXPERIMENTAL CHRONIC PROTEIN INTOXICATION F PENTIMALLI, *Virchows Arch f path Anat* **275** 193, 1930

Pentimalli summarizes his experimental work previously published in Italian and discusses the significance of his observations. In view of the highly toxic action of the derivatives of heterologous proteins, when the latter are suddenly broken down within the body of the sensitized animal, Pentimalli believes it is reasonable to assume that the split products of heterologous proteins should have a toxic action when broken down more slowly over a prolonged period of time. The slow degradation of homologous proteins may be a pathogenic factor in certain human diseases. In his experimental work, Pentimalli used egg albumin, egg yolk and cow's milk, and their derivatives obtained by hydrolytic cleavage in vitro, injecting the material parenterally in small doses every day or on every alternate day into rabbits. Some of the animals died early with anaphylactic manifestations. In others, the injections could be continued over a period of months. These chronically intoxicated animals became cachectic and finally died. The most important changes noted during life occurred in the circulating blood, the most important ones seen after the death of the animals were in the tissues of the hematopoietic system. Many of the animals became anemic, especially those that received egg albumin or its derivatives. The reduction in erythrocytes was often associated with a relative lymphocytosis or monocytosis. The other proteins caused leukocytosis, the increase in the number of leukocytes being due to immature forms of the myeloid or lymphoid series. The leukocytosis was not

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transient, it sometimes persisted for variable periods after the injection of the foreign protein was stopped. The histologic changes in the hematopoietic tissues could be correlated with the altered blood picture.

O T SCHULTZ

COMPARISON OF THE TEMPERATURES OF ANIMALS AFTER THE INJECTION OF BLOOD FROM MALARIAL AND SCARLET FEVER PATIENTS AND FROM NORMAL PERSONS OTTO HERRMANN, *Zentralbl f Bakteriol* **115** 145, 1930

Herrmann injected into four rabbits and forty-five guinea-pigs, either subdurally or subcutaneously, blood from malarial patients or the blood or the brain of other animals already infected by injections from these patients. As controls, eighteen guinea-pigs were similarly given injections of blood from a normal person. Likewise, twenty-three guinea-pigs and eight rabbits were given injections of blood from patients with scarlet fever. In 70 per cent of the cases, increases in the temperature were observed in the animals given injections of blood from the malarial patients, the effects being more constant in the animals given subdural injections. The incubation period varied from four to ten days. The fevers at times lasted for a month, but they quickly disappeared following chemotherapy. Plasmodia were not found in the blood, the brain or the spleen. The animals sickened more frequently after the injection of blood from malarial patients than after injections from patients with scarlet fever.

PAUL R. CANNON

Pathologic Anatomy

THROMBOSIS OF THE HEPATIC ARTERY BERNARD SELIGMAN, *Am J M Sc* **179** 609, 1930

Two cases of thrombosis of the hepatic artery are reported. In one, an acute case, probably secondary to an infection of the biliary tract, there was involvement of the portal and hepatic veins, a hemorrhagic infarct in the liver and thrombosis of the hepatic artery at its bifurcation, extending into the liver. In the other, a more chronic case, probably of atherosclerotic origin in a man with thrombo-angitis obliterans, the main artery was involved, and no infarct was present. The patient probably did not die from this condition. The clinical and experimental evidence suggests that the degree of injury to the liver following occlusion of the hepatic artery depends in part on the site of the occlusion and in part on the extent of the collateral circulation.

AUTHOR'S SUMMARY

FATAL DIABETIC ACIDOSIS LEONA MAYER BAYER, *Am J M Sc* **179** 671, 1930

Six cases of diabetic acidosis, fatal in spite of treatment, have been presented. Clinically, or at autopsy, all these cases were shown to have been complicated by an infective or gangrenous process, in one of them the diabetic syndrome developed secondary to an acute pancreatic necrosis, in one in which treatment included a huge dosage of insulin, there was exhibited an unusual nephrosis. Analysis of the records suggests that death occurred either because treatment was instituted only after intoxication had already progressed too far or because an infection inhibited the power of insulin or because the complication was itself fatal. Experiment with the use of 15 Gm of alkali in four cases showed a significant change in the alkali level in one instance and permanent clinical benefit in none.

AUTHOR'S SUMMARY

BRONCHOLITHS, WITH REPORT OF FOUR CASES JOHN J. LLOYD, *Am J M Sc* **179** 694, 1930

The occurrence of broncholiths was known and reported by the oldest medical observers. The stones probably originate most frequently in an obsolete tuber-

culosis of a bronchopulmonary lymph node in or near the hilus. In a fairly thorough review of the literature in the English language since 1900, reports of eighteen cases were found in addition to the reports of fifteen cases found by West in 1902. Reports of four more are added in this paper, making a total of thirty-seven. The condition probably is more frequent than reported cases would lead one to suppose, as the expectoration of stones may be easily overlooked in the taking of histories, as in case 2 reported in this paper. A calculus that by erosion has entered a bronchus may produce serious results should the stone remain in the bronchus. Perhaps such an occurrence may occasionally account for a post-hemorrhagic spread in tuberculosis as well as the production of a bronchiectasis, lung abscess or empyema.

AUTHOR'S SUMMARY

TERTIARY SYPHILIS OF THE LIVER SIMULATING BANTI'S SYNDROME HORACE MARSHALL KORNS, Am J M Sc 179 811, 1930

A case of tertiary syphilis of the liver which manifested itself as Banti's syndrome in the terminal stages is reported. The literature of tertiary syphilis of the liver reproducing the clinical features of Banti's syndrome is reviewed, from which thirty-six approved cases and thirty questionable cases are collected. One hundred and four additional cases, many of which have been cited frequently in the literature, are excluded from the category. The pathology, semeiology and treatment are discussed briefly. In particular, the great importance of applying the therapeutic test to every case of Banti's syndrome before excluding syphilis as a possible etiologic factor is reemphasized.

AUTHOR'S SUMMARY

ANEURYSM OF THE CORONARY ARTERIES RALPH L. COX and CHESTER D. CHRISTIE, Am J M Sc 180 37, 1930

A case of aneurysm of the right coronary artery is reported. There were no clinical observations suggesting this lesion. In addition to the coronary aneurysm and nodular inequalities in the circumferences of the medium-sized arteries, there were a large saccular aneurysm of the abdominal aorta and a fusiform aneurysm of the right common iliac artery. There was an extreme degree of sclerosis of the coronary arteries, with occlusion of the left ramus descendens and extensive myocardial infarction. This is the thirty-first instance of aneurysm of the coronary arteries that we have found reported in the literature.

AUTHORS' SUMMARY

LIPOMA OF THE MEDIASTINUM WALLACE M. YATER and E. STUART LYDDAN, Am J M Sc 180 79, 1930

Lipoma of the mediastinum is rare, only twelve cases, including the one described in this report, having been recorded as far as could be ascertained. In only one instance was the tumor confined to the mediastinum. In the others, it had grown externally either upward into the neck or through an intercostal space or defect of the sternum to form a tumor of the chest wall, or it had forced its way into one or both sides of the thoracic cavity. Symptoms due to pressure were noted in only four cases. In the case reported here, moderate dyspnea on exertion had been present for eleven years, and the patient died of lobar pneumonia. The lipoma weighed $8\frac{1}{4}$ pounds (41 Kg) and filled the anterior mediastinum, the precordium and the lower two thirds of the right thoracic cavity.

AUTHORS' SUMMARY

MULTIPLE ANEURYSMS OF THE ARTERIES OF THE RIGHT ARM ASSOCIATED WITH ARTERIOVENOUS FISTULA AND ARTERIAL EMBOLISM DWIGHT L. WILBUR, Am J M Sc 180 221, 1930

The association of multiple aneurysms of the right brachial, radial, superficial palmar, common volar digital and volar digital arteries with an embolus in

the radial artery and an arteriovenous fistula of the hand is recorded. This combination of changes is of unusual interest to the physician because of its rarity and because of the many fields that it opens for investigation, and to the surgeon because of the many difficult therapeutic problems that it presents.

AUTHOR'S SUMMARY

UNINFECTED MURAL THROMBI OF THE HEART EARLE A. HARVEY and SAMUEL A. LEVINE, *Am J M Sc* **180** 365, 1930

Uninfected antemortem mural thrombi of the heart were found in 53 per cent of all necropsies at the Peter Bent Brigham Hospital. Cardiac mural thrombi were twice as frequent in males as in females. The majority of these patients died between the ages of 40 and 70 years. The patients with ventricular thrombi following cardiac infarction formed the group of greatest age (62 years). There was a large middle-aged group with valvular disease (45 years). The frequencies of the sites of formation of single mural thrombi were: left ventricle, 31, right auricle, 28, left auricle, 6, and right ventricle, 4. There were forty-two cases of multiple thrombosis. The apexes of the ventricles and the auricular appendages were the most frequent sites of formation of mural thrombi. Secondary infarction outside the heart as a result of emboli occurred with the following frequencies: pulmonary, 47, renal, 18, splenic, 12, and cerebral, 3 (the brain was examined in only a limited number of instances). There were six instances of peripheral arterial thrombosis that may have been embolic. Auricular fibrillation definitely increases the incidence of auricular thrombosis. The two most frequent mechanisms for the formation of cardiac mural thrombi are the myocardial degeneration associated with coronary arterial disease and the improper functioning of the auricles leading to blood stasis. The diagnosis of cardiac mural thrombosis presents difficulties, but this condition should be suspected in cases of coronary thrombosis and chronic valvular disease showing evidence of emboli.

AUTHORS' SUMMARY

THE MUSCULONERVOUS STRUCTURES IN THE SUBMUCOSA OF THE APPENDIX P. MASSON, *Am J Path* **6** 217, 1930

The submucosa of the normal appendix contains muscle bundles, continuous on the one hand, with those of the circular muscle, and on the other hand, with those of the muscularis mucosae. These two muscle groups often anastomose in the middle zone of the submucosa. They are in intimate relation with certain parts of Meissner's plexus. Muscle and nerve together form a complex which may be termed the musculonervous complex of the appendicular submucosa. Under influences that cannot yet be defined, but that are connected, no doubt, with inflammatory crises, the muscle bundles and the nerves become more numerous, acquire more and more intimate relations, and by their accumulation contribute to the thickening of the submucosa. At the same time, the arteries enlarge, their muscle coat hypertrophies, and the arterial nerves become more prominent. The mucosa presents certain changes which in the order of frequency are: decrease in number or complete absence of lymph nodules, scarcity of lymphocytes in the stroma and diffuse hyperplasia of its nerve plexus, to which may be added more localized hyperplasias in the form of ill-defined neuromas or circumscribed neuromas situated in the middle or upper part of the mucosa. In extreme examples there is, in addition, hypertrophy or hyperplasia of the muscle coat and of Auerbach's plexus. To sum up, there are hyperplasia and hypertrophy either of the sympathetic nerves or of the appendicular muscles, or of both, in other words of the motor apparatus of the appendix, together with atrophy of the lymphoid tissue. This series of lesions seems to begin by the formation of these musculonervous complexes.

AUTHOR'S SUMMARY

MULTIPLE INTRACRANIAL ANGIOMAS Kiyoshi Hosoi, *Am J Path* 6 235, 1930

A case of multiple intracranial angiomas associated with multiple intracranial meningiomas all on the right side is reported, with the observations at autopsy. The patient presented no symptoms or signs of definite cerebral localization. The literature on the subject is briefly reviewed.

AUTHOR'S SUMMARY

MENINGIOMAS (MULTIPLE INTRACRANIAL TYPE) Kiyoshi Hosoi, *Am J Path* 6 245, 1930

Two cases of cranial meningioma are here presented: one of multiple dural meningiomas associated with multiple angiomas of the cerebral cortex, and the other, a solitary meningioma with hyperostosis cranii. The tumor cells of the meningioma are mesodermal in origin. They elaborate reticulum, fibroglia, collagen and elastic fibrils. The multiplicity of the intracranial meningiomas and angiomas in case 1 connotes a marked disturbance of the mesodermal germ layer. Clinically and histologically, the meningiomas in these two cases indicate a long drawn-out course. In consideration of the large size attained by these growths, it is remarkable that a tumor of the brain was not suspected. The first case was thought to be a mental case due to the patient's frequent depressive states associated with fits of crying. The second patient, who was under the constant care of a neurologist, was being treated for idiopathic epilepsy. The brain tissue immediately surrounding the meningiomas and the angiomas and also far removed from these growths showed no reactive increase in microglia or oligodendroglia, although in the adjacent cerebral cortex in both cases, so-called "amyloid" bodies were abundant. A reactive gliosis was present in the tissue adjacent to the ventricular tumor.

AUTHOR'S SUMMARY

NEPHROSIS IN MULTIPLE MYELOMA David Perla and Laurence Hutner, *Am J Path* 6 285, 1930

Two instances of multiple myeloma with severe nephrosis and shrinkage of the kidney are reported. A review of the literature reveals several other similar instances. A study of the pathologic changes of the kidneys in instances of multiple myeloma associated with Bence-Jones albumosuria is made. From this analysis it is concluded that the pathologic changes found in the kidney in multiple myeloma consist of three distinct elements, no one of which is constantly present but all three of which may be present: a nephrosis specifically associated in some way with the Bence-Jones albumosuria and the myeloma, arteriosclerosis of the kidney, an independent vascular disease of the kidneys, present in a milder or severer form in almost every instance of multiple myeloma occurring in the age group of from 50 to 70 years, and calcium deposits in the kidney tubules dependent on a destruction of bone and the release of large quantities of calcium in the blood. Clinically, the nephrosis differs from the idiopathic type in the absence of edema, in the increase in the concentration of nonprotein nitrogen in the serum and in the inability to concentrate urine, with a consequently low specific gravity of the urine. Anatomically, the nephrosis is severe and the kidneys are contracted. The kidneys are small and pale with smooth surface and markedly narrowed cortex. Microscopically there is extensive destruction of the tubules of the cortex and medulla, with replacement by dense cellular fibrous tissue. Though there is some hyalinization of a few glomeruli, this lesion is apparently associated with a concomitant arteriosclerosis, the primary lesion being the destruction of the tubules.

AUTHORS' SUMMARY

HISTOLOGICAL CHANGES IN THE RENAL GLOMERULUS IN ESSENTIAL HYPERTENSION Leone McGregor, *Am J Path* 6 347, 1930

The glomerular lesion of essential hypertension is as typical as the arteriolar lesion. It consists of a decrease in size and a simplification of the glomerulus,

with a marked thickening and wrinkling of the glomerular basement membrane. In this series of fifty-one cases, the average percentage of such glomeruli is 47 in the renal group (death from uremia), 33 in the cardiac group (death from myocardial insufficiency or coronary disease) and 24 in the cerebral group (death from apoplexy). The arteriosclerosis precedes, and is related to the change in the glomerular basement membrane. Kidneys from persons dying in the fifth, sixth, seventh and eighth decades with a history of normal blood pressure show 96.2 per cent normal glomeruli. A rare hypertensive contracted glomerulus may be found. There are inflammatory glomeruli in any type of essential hypertension, but they are most numerous in the renal group. The lesions are usually focal, and as many as 15 per cent of the glomeruli may be involved. Aniline blue (Mallory-Heidenhain azan carmine) is recommended as a routine stain for kidney tissue. It is particularly helpful to differentiate the renal group of cases of essential hypertension from cases of chronic glomerulonephritis that present extensive vascular disease.

AUTHOR'S SUMMARY

A CASE OF LYMPHOBLASTOMA, HODGKIN'S DISEASE AND TUBERCULOSIS H. E. MACMAHON and F. PARKER, JR., *Am J Path* 6 367, 1930

A case is described of an elderly patient who was admitted to the hospital with the diagnosis of aleukemic leukemia. He was watched over a period of three years, and during that time a manifest lymphatic leukemia developed. Following a short but severe infection, his white blood count and differential values returned to normal and remained unchanged till his death a year and a half later. Autopsy showed that he had not only aleukemic leukemia, but also Hodgkin's disease and generalized tuberculosis.

AUTHORS' SUMMARY

MARKED DILATATION OF THE LEFT AURICLE OF THE HEART E. A. BURKHARDT, JR., *Am J Path* 6 463, 1930

The auricular dilatation described is associated with mitral stenosis of rheumatic origin. Many cases show more marked mitral stenosis with little or no auricular dilatation. Emanuel expressed a belief that the auricular dilatation is due to auricular myocardial damage. To prove this point he described a heart in St. Bartholomew's Hospital Museum, the left auricle of which is markedly dilated yet the mitral valve of which admits three fingers. A heart in the University College Hospital is similar, the mitral valve of which is only slightly thickened. Bach and Keith presented a heart with marked left auricular dilatation, the mitral valve of which admits three fingers. This case, however, as most cases cited in the literature, presents pericarditis with the valvular lesions. This reaction is symbolic of a pancarditis that includes the myocardium of the left auricle. Increased intra-auricular pressure through an incompetent mitral valve plus a damaged myocardium probably accounts for marked left auricular dilatation.

AUTHOR'S SUMMARY

HISTOLOGICAL STUDIES ON THE BRAIN OF A CRANIOPAGUS K. LOWENBERG, *Am J Path* 6 469, 1930

The case described belongs in the group of craniopagus parietalis. The malformation is confined to the skull and brain. The brain of the child "A" is asymmetrical and shows pronounced malformation of the gyri and sulci, which makes the identification of the latter difficult. Many sulci are absent. The general outlines of the brain are like those in a 7 or 8 months old fetus. Histologically, both the granular and the agranular six-layer types of cortex are present. In the precentral region, the fourth layer is still granular in structure, which corresponds to the development of the eighth month of intra-uterine life.

AUTHOR'S SUMMARY

CONGENITAL ANEURYSM OF THE INTERVENTRICULAR SEPTUM D E CANNELL,
Am J Path 6 477, 1930

The clinical and pathologic observations in two cases of congenital aneurysm of the interventricular septum are here reported. The absence of clinical signs and symptoms in both cases, wherein marked distortion of the normal anatomy was present, is remarkable. A critical study of these cases adds further evidence in favor of these anomalies being congenital malformations, rather than the terminal results of endocarditis.

AUTHOR'S SUMMARY

RENAL LESIONS WITH RETENTION OF NITROGENOUS PRODUCTS PRODUCED BY
MASSIVE DOSES OF IRRADIATED ERGOSTEROL TOM DOUGLAS SPIES and
EUGENE C GLOVER, Am J Path 6 485, 1930

The administration of massive doses of viosterol to rabbits caused marked histologic changes in the kidneys. The chief changes were sclerosis and hyalinization of the walls of blood vessels, and thickening of the basement membranes of the tubules and glomerular capsules, accompanied in both by extensive sub-epithelial deposits of hyalin. There was abundant deposition of calcium in these localities. Pronounced atrophy of the tubular epithelium also occurred. The lesions were accompanied by the appearance of large amounts of albumin in the urine and by retention of nitrogenous products in the blood. The degree of nitrogen retention was in general proportional to the amount of damage of the kidney, as evidenced by histologic examination.

AUTHORS' SUMMARY

METASTASIZING "CARCINOID" TUMOR OF JEJUNUM ISTVAN GASPAR, Am J
Path 6 515, 1930

A case of multiple carcinoid tumors of the jejunum, one of which caused intestinal obstruction, with metastases in the mesentery and liver, is reported. Histologic examination revealed the picture of typical carcinoid tumor. Serial sections definitely indicate that at least two of the tumors originated in the crypts of Lieberkuhn. Positive silver impregnation of the tumor cells confirms Masson's contention that the origin of carcinoid tumors is in the Nicholas-Kulchitzky-Masson cells in the glands of Lieberkuhn. Carcinoid tumors may assume clinical significance.

AUTHOR'S SUMMARY

SMALL CELL CARCINOMAS OF THE LUNG HOWARD T KARSNER and OTTO
SAPHIR, Am J Path 6 553, 1930

Small cell primary tumors of the lungs or bronchi are epithelial in character, as indicated by cell arrangement, relation of connective tissues and blood vessels and complete absence of capacity to form reticulum. Small cell cancers of the lung originate in bronchi or bronchioles and are probably unicentric in origin. Small cell cancers of the lung more frequently produce large mediastinal masses than do other cancers of this organ and are firmer in consistency, but in other clinical and gross pathologic aspects show no distinctive characters.

AUTHORS' SUMMARY

MULTIPLE GUMMAS OF THE HEART IN THE NEW BORN JOHN W WILLIAMS,
Am J Path 6 573, 1930

A case of gumma of the heart in a Negro infant that died a few hours after birth is reported. The term gumma as descriptive of the lesion is questioned, since the microscopic picture is at variance with that of gumma. The terms "localized syphilitic cellulitis" and "fulminant syphilitic myositis" are suggested in its stead as descriptive of this lesion, since it is characterized by destruction of muscle and infiltration with lymphocytes, polymorphonuclear leukocytes, monocytes and plasma cells.

AUTHOR'S SUMMARY

MULTILOCLULAR CYST OF THE SPLEEN PRODUCED BY INFARCTS W DOBRZANIECKI, Ann Surg 92 67, 1930

Cysts of the spleen may be of the dermoid type, or they may have their origin from inclusions of peritoneum that undergo secondary degeneration, in other instances, the dilated spaces have been shown to be of lymphatic derivation. Previous abscesses, inflammatory processes about the spleen and trauma have been the causative factors in some cases. The author reports the occurrence, in a woman, aged 38, of a cyst of the spleen, measuring 25 by 13 by 14 cm, which contained 140 cc of amber-colored, transparent fluid that coagulated after removal. He attributes the process to obliterative endarteritis, with necrosis and infarction, as the result of emboli.

RICHARD A LIFVENDAHL

ACUTE ULCERATION OF THE STOMACH IN CHILDREN B R SHORE, Ann Surg 92 234, 1930

The literature of the subject is reviewed and the following case reported. The posterior fundic wall showed a perforation 3 cm wide, which represented an ulcer that had penetrated. The ulcer was characterized by necrotic edges in which the submucosa and the muscularis were swollen and edematous and showed thrombosed vessels. The abdominal cavity contained free air and fluid. For several days previous to the perforation the child had had a "running nose," but there was also a history of its having swallowed some broken glass at the age of 22 months. The glass, however, was not found at operation or at autopsy.

RICHARD A LIFVENDAHL

INTRA-ARTICULAR ENDOTHELIAL TUMORS ARISING FROM SYNOVIAL MEMBRANE L C WAGNER, Ann Surg 92 421, 1930

From the knee of a man, 35 years old, a hard, encapsulated, yellowish-brown tumor, 7 by 5 by 3 cm, was removed, which had the gross appearances of a fibroma, but which microscopically was regarded as a fibro-endothelioma, most likely arising from the endothelial cells lining the bursa. Although treatments with the x-rays and Coley's toxin were given, local recurrences were present within two years, necessitating a mid thigh amputation. A second case of intra-articular endothelial tumor arising from the synovial membrane occurred in the ankle joint of a girl 15 years of age. These 2 cases represent the only ones in 467 explorations of major joints of the body.

RICHARD A LIFVENDAHL

MULTIPLE MYELOMA AS A SINGLE LESION C F GESCHICKTER, Ann Surg 92 425, 1930

The two cases of multiple myeloma as a single lesion reported substantiate the claim for consideration of multiple myeloma in the differential diagnosis of single lesions of bone, one occurred in the femur and the other in the clavicle. In the former, no other bones were involved at the time of writing, no Bence-Jones protein was found in the urine, there was no lumbar backache with signs of early paraplegia, the hemoglobin and erythrocyte determinations were normal, and there were no evidences of nephritis with nitrogenous retention. Thus, the six cardinal diagnostic points were violated. Giant cell tumors, metastatic carcinoma, chloroma and myxochondroma were considered in the differential diagnosis.

RICHARD A LIFVENDAHL

GASTRIC SEQUELAE OF CORROSIVE POISONING WILLIAM S BOIKAN and HARRY A SINGER, Arch Int Med 46 342, 1930

The ingestion of acid, even in relatively small quantities or low concentrations, may be followed by stenosis of some part of the stomach without esophageal

involvement The swallowing of lye leads to esophageal obstruction associated frequently with gastric obstruction, rarely to gastric obstruction alone Organic obstruction of the stomach does not occur immediately, but usually manifests itself several weeks after the recovery from the initial effects has been considered complete Late gastric stenosis should be anticipated in all cases of corrosive ingestion (especially when the substance is known to be an acid), even though the patient is restored to complete health shortly after the poisoning The type and location of the lesion in the upper part of the gastro-intestinal tract can be predicted from a knowledge of the corrosive ingested, whether acid or alkali, and the state of the stomach, whether empty or full In late cases of cicatricial stenosis of the stomach, gastro-enterostomy is the operation of choice In early cases in which an active inflammation exists, a preliminary jejunostomy is often advisable

AUTHORS' SUMMARY

SPONTANEOUS RUPTURE OF THE NORMAL SPLEEN W H BYFORD, Arch Surg
20 232, 1930

A search of the literature revealed eight cases of spontaneous rupture of the normal spleen The symptoms are those of severe abdominal pain followed by shock, evidences of hemorrhage, pain radiating to the shoulders, and tenderness and vomiting, therefore similar in every respect to traumatic rupture of the spleen, with the absence of the traumatic etiology The spleen in the reported case weighed 156 Gm and measured 17 by 18 by 2 cm Much of the hemorrhage was subcapsular The microscopic section failed to reveal any pathologic change in the parenchyma The author reviews the various theories, most of which hold a diseased spleen to be the primary factor The author, however, feels that spontaneous rupture of the normal spleen occurs

N ENZER

CONGENITAL CYSTIC LUNG IRVING J WOLMAN, Bull Ayer Clin Lab of
Pennsylvania Hosp, 1930, no 12, p 49

A case of congenital cystic lung in a six months' stillborn fetus, discovered in the course of a routine necropsy, is recorded The author holds that the cystically dilated intercommunicating bronchioles and aveoli form a closed system, or systems of chambers, not continuous with the main bronchi

METAPLASIA IN THE LYMPH NODES AND SPLEEN IN A CASE OF MYELOGENOUS
LEUKEMIA WEBB HAYMAKER, Bull Ayer Clin Lab of Pennsylvania Hosp,
1930, no 12, p 55

A case of leukemia is described in which there was marked extramedullary hematopoiesis The relative aplasia of the bone-marrow, particularly in the formation of erythrocytes, together with the numerous islands of developing erythroblasts and granuloblasts in the spleen and lymph nodes, leads to the assumption that these organs had returned to their embryonic function of producing myeloid cells Further evidences supporting the view of metaplasia and opposing that of mere colonization were the size and the homogeneity of the spleen and the absence of clumps of myeloid cells in other organs

AUTHOR'S SUMMARY

HISTOLOGICAL CHANGES IN NERVE CELLS FOLLOWING INJURY ORTHEILO R
LANGWORTHY, Bull Johns Hopkins Hosp 47 11, 1930

The nerve cell injuries that are discussed here involve both the nucleus and the cytoplasm The nucleolus is considered to be very resistant, but a marked swelling of this structure may be seen in the cells When death occurs immediately from electrical injuries, many of the cells have nuclei that are shrunken and that stain a uniform deep color, so that nucleolus and chromatin strands may no longer be distinguished The nucleus is often displaced to one side of the cytoplasm and

is surrounded by a pale area indicating its former size. The suggestion is made that cells with deep-staining shrunken nuclei have no longer the power of recovery. Abnormalities following less severe damage of the nerve cell are illustrated. The cytoplasm of the injured cells is shrunken, and the perivascular space is large. Immediately following the trauma, there is a considerable decrease in Nissl substance, and that which remains has lost its flaky appearance and looks coarsely granular. Often the edges of the cytoplasm appear to have no continuity, as if the cell had ruptured into the perivascular space. Swelling of the nucleolus occurs. A few hours after the electric shock the whole cytoplasm stains a uniform, deep color and no granules may be found. The Nissl substance is gradually reformed over a period of days, sometimes appearing first in the periphery of the cell and sometimes in the center around the nucleus. Restitution of the nucleus takes a longer time. Cells that are injured beyond possibility of recovery become greatly shrunken, and cytoplasm and nucleus stain a uniform black color. Such cells are removed by phagocytosis. The electrical current has a selective effect on the nerve cells, some anterior horn cells are greatly injured while others are fairly normal.

AUTHOR'S SUMMARY

THE PLACENTA FROM A CASE OF MALARIA. GEORGE B. WISLOCKI, Bull. Johns Hopkins Hosp. **47** 157, 1930.

The study of the placenta in a case of malaria affords proof that the chorionic syncytium is incapable of phagocytosing an inert suspension of pigment present in the intervillous spaces or of transmitting such particles from mother to fetus. Malarial parasites are present in the placenta in great abundance within the erythrocytes in the intervillous spaces. Malaria induces the accumulation of large numbers of monocytes and lymphocytes in the placental circulation. Of these cells, the monocytes phagocytose, abundantly, pigment released by the activity of the malarial organisms. These phagocytic monocytes do not penetrate the fetal tissues, but enter the masses of fibrin formed on the villi, which are denuded of syncytium at these sites. Typical clasmatoocytes are not encountered in the intervillous spaces. The monocytes and lymphocytes that gather in the placenta are brought there from other parts of the maternal body where they are produced. The villi, including their stroma and covering chorionic syncytium, are anatomically normal and not visibly affected by the malarial organisms or by their products. It is unlikely that malarial organisms can enter or penetrate the chorionic syncytium, so that the transmission of malaria from mother to fetus occurs rarely, if at all.

AUTHOR'S SUMMARY

ANASTOMOSIS OF THE HEPATIC AND PORTAL CIRCULATIONS. JOHN MCKEE OLDS and EDWARD STEPHENS STAFFORD, Bull. Johns Hopkins Hosp. **47** 176, 1930.

The hepatic artery communicates by means of capillaries directly with the sinusoids of the liver lobule at the periphery of the lobule. The portal vein also communicates directly with the hepatic sinusoids at the periphery of the lobule. There are no interlobular capillary anastomoses between the hepatic artery and the portal vein. The capillaries of the bile duct plexuses (branches of the hepatic artery) communicate directly with the hepatic sinusoids at the periphery of the lobule. No translobular arteries can be demonstrated. Mixing of hepatic arterial and portal venous blood occurs via the outermost or peripheral sinusoidal anastomoses, but not within the interlobular tissue itself.

AUTHORS' SUMMARY

ASBESTOSIS BODIES IN SPUTUM AND LUNG. K. M. LYNCH and W. A. SMITH, J. A. M. A. **95** 659, 1930.

In microscopic sections of lung from the body of a worker in an asbestos factory, who died from a gunshot wound, numerous asbestosis bodies were found.

in the alveoli, the walls of the alveoli, the deeper pleural tissues, the bronchi, and the interlobular framework, in thrombi in the veins and in the peribronchial lymph glands. Associated with them were black granular pigment, in the lymph glands a yellow-brown granular substance, a reaction of mononuclear and polymorphonuclear giant cell phagocytes and in the framework structures a cellular increase in fibrous tissue. The asbestosis bodies were seen in the sputum of three people who had been workers, in an asbestos factory, one as long before as six years. In the sputum, these bodies had a central filament of a transparent, slightly greenish-tinged, needle-like crystal. On this were deposited nodules, blebs and segments of a homogeneous refractive substance. These bodies were from 12 to 140 microns long and from 1 to 12 microns thick. They did not take the ordinary dyes for tissue and sputum. They could be stained by the prussian blue reaction for iron. It is suggested that the iron content of the deposit was of tissue origin, probably from the blood.

GEORGE RUKSTINAT

INTRANUCLEAR BODIES IN RENAL DISEASE OF CALVES THEOBALD SMITH,
J Exper Med **51** 519, 1930

Renal lesions chiefly the result of obstructive processes were associated with intranuclear bodies in the epithelium of straight and convoluted tubules. In one animal these bodies were found in large numbers in otherwise still normal organs. The affected animals had been fed cow serum in place of colostrum.

AUTHOR'S SUMMARY

DOUBLE VITAL STAINING WITH BRILLIANT VITAL RED AND NIAGARA SKY
BLUE F B DAVIES, R C WADSWORTH and H P SMITH, J Exper Med
51 549, 1930

Vital staining reactions of brilliant vital red and Niagara sky blue are studied in dogs and in rabbits. Either dye alone is taken up to form red or blue granules within the cytoplasm of macrophages and of certain other cell types. When the two dyes are injected simultaneously into the blood stream one finds that these cells build up granules which are purple from admixture of the two dyes. When several daily injections of one dye are followed by several daily injections of the other, one finds blue granules and red granules side by side within the cells, but no purple granules are found. This is thought to indicate that the dye is deposited in small foci which are active in a rather transitory way, and that the color of the granule is determined during its formative stage by the type of dye present in the fluids about the cell. The enlargement of phagocytic cells and the increase in their number with large dosage, or with repeated offerings of the dye, represent a method by which the cells maintain their phagocytic powers at the normal level. Evidence is offered to indicate that these and perhaps other compensatory changes may take place with great rapidity, so that it has been impossible to "block" or even reduce noticeably the ability of these cells to take up additional quantities of dye. Certain pitfalls in the experimental study of "blockade" are pointed out.

AUTHORS' SUMMARY

THE EFFECT ON THE RATE OF UREA EXCRETION OF CARMINE DEPOSITION IN
THE CELLS OF THE RENAL TUBULES EATON M MACKAY and LOIS
LOCKARD MACKAY, J Exper Med **51** 609, 1930

The evidence that urea is present in high concentration in the cells of the convoluted tubules of the kidney and is passing through these cells has been reviewed. Following the deposition of a large amount of carmine in the cells of the convoluted tubules the rate of urea excretion, as measured by the relation of the rate of urea excretion to the blood urea concentration, is increased. This is interpreted as due to blockade or damage to the cells of the convoluted tubules which interferes with their usual function of absorption of urea and other sub-

stances from the glomerular filtrate and hence increases the amount of urea which reaches the bladder urine at a given blood urea concentration

AUTHORS' SUMMARY

ABNORMALITIES PRODUCED IN THE CENTRAL NERVOUS SYSTEM BY ELECTRICAL INJURIES ORTHEILO R. LANGWORTHY, J. Exper Med **51** 943, 1930

The alternating and continuous circuits produced different types of lesions in the central nervous system. Hemorrhages were common after alternating current shocks and few hemorrhages were observed in the continuous circuit group. With both types of circuits at 1,000 and 500 volts potential, severe abnormalities in the nerve cells were observed. These were more marked in the continuous circuit group. A uniformly staining, shrunken, pyknotic nucleus was taken as a criterion of nerve cell death. The Purkinje cells of the cerebellum were most susceptible to the current. Injured cells were studied in the dorsal nucleus of the vagus, in the somatic motor group, among the primary sensory neurons and in the olives. Changes in the histologic structure of the cells in reference to recovery have been discussed. Injury to the cerebral and cerebellar cortices occurred on the dorsal surface close to the head electrode. Small cavities were produced, particularly in the cerebral cortex, as the result of the circuit contract. With the continuous and alternating circuits at 110 and 220 volts potential, less severe changes were observed in the nerve cells although hemorrhages were common in the alternating circuit group. It must be assumed in these cases that death was due to respiratory block rather than to actual death of the cells.

AUTHOR'S SUMMARY

BLOOD CYTOLOGY OF THE RABBIT LOUISE PEARCE and ALBERT E. CASEY, J. Exper Med **52** 145 and 167, 1930

The periods of greatest irregularity in mean neutrophil and eosinophil values occurred in the fall and the late winter and spring months of both years during which observations were made, but in the case of the basophils, the irregularities were distributed throughout the first year and occurred chiefly in the winter months of the second year. The major trends, and many of the minor fluctuations, as well, which were observed in the mean cell values of one group of rabbits were also generally seen in another group examined during the same months. The general levels of the neutrophil, basophil, and eosinophil mean values were higher in the groups examined during 1927 and 1928 than in the examined groups during 1928 and 1929. The general levels of the lymphocyte and monocyte mean values were higher in the groups examined during 1927 and 1928 than in the groups examined during 1928 and 1929. The results based on the trends of mean group values, obtained from consecutive weekly observations, showed no evidence of a consistent numerical relationship between lymphocytes and monocytes.

AUTHORS' SUMMARY

EXPERIMENTAL NEPHRITIS IN THE FROG JEAN OLIVER and PEARL SMITH, J. Exper Med **52** 181, 1930

The damage produced by corrosive mercuric chloride, U. S. P., potassium bichromate and uranium nitrate in the frog's kidney is described. The morphologic lesions consist of tubular damage, such as regressive changes in the epithelium, and of damage to the glomeruli, ranging from increase in their permeability to gross damage of, and hemorrhage from the tuft. The point is emphasized that these lesions differ in their degree, rather than in their nature, from those found in the mammalian kidney after the administration of the same poisons. The frog's kidney is exceptionally well suited, therefore, for the study of lesions which, though present, are masked in the complexities of structure and function of the mammalian kidney.

AUTHORS' SUMMARY

THE ORIGIN AND FATE OF TWO TYPES OF MULTINUCLEATED GIANT CELLS IN THE CIRCULATING BLOOD CLAUDE E FORKNER, J Exper Med **52** 279, 1930

It has been demonstrated that giant cells of the foreign body and epithelioid types can be induced to appear in the blood stream. Evidence has been presented which indicates that foreign body giant cells are primarily formed by fusion of monocytes, and that the fate of these giant cells is accomplished, at least in some instances, by a separation into the constituent elements. Further evidence has been presented which lends support to the hypothesis that "epithelioid giant cells" reach their stage of evolution, not by fusion of monocytes, but by amitotic division of the nuclei of monocytes and epithelioid cells. The presence of giant cells in the peripheral blood as the result of injections of agar is almost invariably associated with, or preceded by, a marked monocytosis in which the new monocytes are of large size and show evidence of immaturity. Injections of agar into the tissues result in decreased absolute and percentage values of lymphocytes and a diminution of the specific granules in many of the polymorphonuclear leukocytes. It would appear from these studies that a clear differentiation of "epithelioid giant cells" and "foreign body giant cells" in the blood is usually possible, but that, on the other hand, a few cells may be present which have some of the characteristics of each type. The latter probably represent in their formation both a fusion of individual cells and an amitotic division of the nuclei of monocytes. Clasmatocytes or macrophages have in rare instances been seen to take part in the formation of foreign body giant cells. At least one instance has been noted of the fusion of a clasmatocyte with several monocytes. No evidence is available to demonstrate that macrophages ever play a part in the formation of "epithelioid giant cells".

AUTHOR'S SUMMARY

GENETIC RELATIONS OF MONOCYTES CLAUDE E FORKNER, J Exper Med **52** 385, 1930

The theories for the origin of monocytes from myeloblasts, lymphocytes, endothelium, macrophages and primitive cells are reviewed and considered. Monocytes in all stages of development have been demonstrated to be present constantly in large numbers in all the lymph nodes of the body, except in the large mesenteric group. The relations of these cells to undifferentiated cells, lymphocytes, macrophages, plasma cells and endothelium are described. The origin of adult monocytes from primitive undifferentiated cells through the stages of monoblasts and premonocytes is described and illustrated. The demonstration in certain lymph nodes of innumerable monocytes in all stages of development permits a shifting of the term "monoblast" from the position of a more or less theoretical name to its proper place as a term designating that particular cell which is derived from a primitive undifferentiated cell and which is the immediate precursor of the premonocyte. The term "premonocyte" is proposed to designate the intermediate stage between the monoblast and the mature monocyte. Evidence is advanced to show that monocytes are an independent strain of cells, but that under physiologic conditions they may be transformed into macrophages, thus representing at least one way in which the latter are normally produced. In no organs or tissues other than in certain specific lymph nodes, chiefly the peripheral group, can one constantly find monocytes in all stages of development. Developing monocytes occasionally may be found in small numbers in the spleen, mesenteric lymph nodes, Peyer's patches, subcutaneous connective tissues, lungs and omenta of normal rabbits but their presence is by no means constant and their numbers are insignificant in comparison with those found in the peripheral lymph nodes. Monocytes and premonocytes do not stain by the common methods used for the demonstration of the reticulo-endothelial system and therefore must be considered for the present as independent of this system, except so far as monocytes may be transformed into macrophages. Plasma cells, stained with the supravital technic, as seen in

lymph nodes, are described. No basis has been found for the theory that plasma cells and monocytes are closely related structural elements.

AUTHOR'S SUMMARY

AN ANATOMICAL STUDY OF SUBDURAL HEMORRHAGE ASSOCIATED WITH TENTORIAL SPLITTING IN THE NEWBORN W H CHASE, Surg Gynec. Obst **51** 31, 1930

This communication contributes an etiologic and anatomic analysis of a series of thirty-two cases of subdural hemorrhage associated with tentorial splitting in the new-born infant. The blood is largely supratentorial and often bilateral as a result of stretching or rupturing of the small tributaries of the great cerebral vein near its junction with the straight sinus. The most important predisposing factor to intracranial hemorrhage and tentorial splitting is prematurity, in that the dural septal fibers are of greater immaturity. The method of examination, the anatomy and the clinical aspects are adequately discussed.

RICHARD A LIFVENDAHL

LIPIODOL PELVIC CYSTS A F LASH, Surg Gynec Obst **51** 55, 1930

Few instances of nonabsorption or untoward effects of iodized poppy seed oil 40 per cent have been reported, although this opaque medium has been used in the spinal and cerebral spaces, genito-urinary organs and pericardial, pulmonary, joint and peritoneal cavities. The presence of an infection of the female generative tract is regarded as a contraindication to the use of this diagnostic medium, for the oil has not been demonstrated to have antiseptic properties, a foreign body reaction may be induced in the pelvis. In the author's case, this occurred after injection of the oil into a uterus bicornis unicollis associated with chronic salpingitis, although the function of the tubes was not disturbed by the iodized oil, as the patient delivered a full term child one year after the injection. Laparotomy, twenty-two months after the diagnostic injection, revealed pelvic adhesions in which were cysts filled with clear, light amber, oily fluid, and surrounded each by a connective tissue capsule lined by histiocytes and foreign body giant cells outside of this capsule.

RICHARD A LIFVENDAHL

URETHRAL CARUNCLE IN THE FEMALE C T OLCOTT, Surg Gynec Obst **51** 61, 1930

These dusky red pedunculated or broad-based growths of the lower half of the external urethral orifice are frequently regarded as malignant because of the marked infolding of the epithelium. In seventeen of twenty-three cases, a definite glandular mass was present in the submucosa, and to the author represented glands of Skene and therefore an important factor in the formation of caruncles.

RICHARD A LIFVENDAHL

GELATINOUS DEGENERATION OF THE BONE MARROW PAUL MICHAEL, J Path & Bact **33** 533, 1930

Eleven cases of "gelatinous degeneration" of the bone-marrow were seen in 480 autopsies. In 4 of the 11 cases, tuberculosis was the cause of death, in 3, carcinoma, in 1 each, pyemia, degenerative productive nephritis, lymphogranulomatosis and ulcerative colitis. The average age was 40.1 years. The average duration of disease was 15.7 months. The proportion of males to females was 10:1. Gelatinous degeneration differs from uncomplicated edema of the bone-marrow in the presence of precipitated fibrin about the periphery of the fat cells. It is apparently the result of a reaction of fat and edema in the presence of fibrinogen, and should be considered as a lesion *suu generis* of the bone-marrow—best expressed as "hydrops fibrinosus of the bone-marrow." The latter expression should replace the indefinite term "gelatinous degeneration."

AUTHOR'S SUMMARY

ENDOMETRIAL AUTOTRANSPLANTS IN THE RABBIT H H GLLAVE, J Path & Bact **33** 675, 1930

The histologic appearance of autotransplants of endometrial tissue in the rabbit corresponds to that of the uterus of the same animal Under the influence of the corpus luteum hormone (estrin) or after oophorectomy they show the same changes as the uterus

AUTHOR'S SUMMARY

VITAMIN D SCLEROSIS IN THE RAT'S AORTA J B DUGLID, J Path & Bact **33** 697, 1930

The essential lesion of vitamin D sclerosis is a degeneration of muscle and calcification of the media similar to that seen in experimental adrenalin lesions in rabbits and in Mönckeberg sclerosis of the peripheral arteries in man A secondary overgrowth of the intima from proliferation of intimal cells arises only when the adjacent subintimal layers are degenerate It is a reparatory measure, and occurs when gross mechanical destruction is caused by masses of calcareous material in the subintimal layers being uprooted and thrust into the intima by the movements of the wall of the vessel Fatty changes are secondary, and similar to the fatty changes seen in human atheroma They occur most frequently in the subintimal layers of the media, and are associated with mechanical disturbances, such as shearing and stressing of the tissues between one layer and another

AUTHOR'S SUMMARY

ATROPHY OF THE ADRENALS ASSOCIATED WITH ADDISON'S DISEASE WILLIAM SUSMAN, J Path & Bact **33** 749, 1930

Five cases of Addison's disease are recorded, in which the lesion in the suprarenal glands was a simple or fibroid atrophy, and it is found that about one fifth of all cases of Addison's disease are associated with this form of lesion Atrophy of the suprarenal glands as a cause of Addison's disease appears to be more common in England than elsewhere In cases of atrophy, both cortex and medulla are usually affected, but a lesion of the cortex is the more constant and in some cases may be the sole feature

ADRENAL ATROPHY AND ADRENAL TUBERCULOSIS IN RELATION TO ADDISON'S DISEASE F F HELLIER, J Path & Bact **33** 761, 1930

In 12,000 consecutive necropsies, 12 cases of Addison's disease occurred, in 6 of which there was tuberculosis, and in 3 atrophy, of the suprarenal glands

ADRENAL ATROPHY IN ADDISON'S DISEASE W G BARNARD, J Path & Bact **33** 765, 1930

In twenty-three cases of Addison's disease examined post mortem, the suprarenal glands were tuberculous in sixteen and atrophied in seven

FIBRIL FORMATION OF EPITHELIOID CELLS IN TUBERCULOUS TISSUE I WALLGREN, Arb a d path Inst zu Helsingfors **6** 51, 1930

In tubercles, as well as in tuberculous granulation tissue, there is a rich formation of fibrils which do not stain by the usual methods, but which appear after impregnation with silver nitrate The fibrils lie in the ectoplasm of the cells and resemble those of the fetal mesenchyme There are apparently two types of epithelioid cells Those originating from reticulo-endothelium are capable of forming fibrils, those originating from lymphoid cells are not As these fibrils mature, they sometimes stain with fuchsin and also seem to undergo hyaline degeneration These fibrils are not fibrin Their formation may influence healing in certain tuberculous lesions

GEORGE RUKSTINAT

AN ABERRANT ADENOMA OF THE THYROID GLAND P E A NYLANDER, Arb
a d path Inst zu Helsingfors 6 235, 1930

Nylander found a "struma, nodosa colloides, macrofolliculars papillaris," in an aberrant portion of thyroid gland The tumor started to develop several months after thyroidectomy in a man

GEORGE RUKSTINAT

EXPERIMENTAL ACUTE DIFFUSE GLOMERULONEPHRITIS R HUCKEL, Beitr z
path Anat u z allg Path 84 571, 1930

In agreement with Vollhard, Fahr, Lichtwitz and others, the author recognizes two forms of glomerulonephritis, the localized and the diffuse In the former a single capillary loop of the glomerulus is involved, or at most the capillaries of a lobule are involved, whereas in the diffuse form the entire capillary tuft takes part in the process In the early stages of the latter, as seen in the human kidney, the glomerulus is increased in size, and the entire capillary tuft is swollen and exhibits an increased nuclear content, due in part to leukocytes within the capillary lumen and in part to endothelial proliferation The capillaries contain little or no blood Fahr has held inflammation of the tuft to be the primary and essential process in diffuse glomerulonephritis, whereas Vollhard and others have considered spasm of the afferent arteriole primary, to which the involvement of the tuft is secondary Localized glomerulonephritis, which may be embolic and non-purulent, bacterial as the result of the excretion of bacteria by the glomerulus, or toxic, may be produced experimentally The author claims that the diffuse form has not been successfully reproduced experimentally Experimental reproduction of the lesion is desirable because it would permit study of the early stages of the process, concerning which there is considerable dispute Huckel used scarlet fever streptococcus toxin (Dick toxin), injecting it directly into the exposed renal vein, the injection being directed toward the kidney At this point it may be noted that, as far as one may determine from the article itself, in his series of experiments he used only six rabbits, one of which served as a control for the injection into the renal vein of physiologic solution of sodium chloride in an amount equal to that used in the experiments with toxin Two animals received 35 cc of 1 100 toxin and 3 cc of 2 100 toxin, respectively, and died after thirty-seven and nine and one half hours Another animal received 1 cc of undiluted toxin and was killed after sixteen hours In the remaining two experiments, several days were allowed to elapse after a single or repeated injections in order to study the later stages of the process The changes noted were increase in the volume of the capillary loops of the tufts, increased intracapillary cellularity due to what the author terms intracapillary exudation, slight proliferation of the endothelium and hyperemia These changes, which are characteristic for human diffuse glomerulonephritis, in the absence of detectable alterations in the afferent vessels, the author considers proof that the process is primarily an inflammation of the capillary tuft Although in the experiments of longer duration there were noted changes comparable with the later stages of human glomerulonephritis, the most striking reaction was a diffuse interstitial sub-acute inflammatory process

O T SCHULTZ

ACUTE PEPTIC DUODENITIS H RADECKE, Beitr z path Anat u z allg Path
84 617, 1930

As a contribution to the contention of the Aschoff school that the gastric juice may exercise a caustic action and may cause localized erosions and ulcerations from which the typical peptic ulcer of the stomach may develop, Radecke presents a study of lesions encountered post mortem in the duodenum in three cases The lesions were most numerous in the upper part of the duodenum and were absent at and below the level of the papilla of Vater They were localized and not diffuse and were situated on the crests of the rugae of the mucosa of the anterior and posterior walls of the duodenum The earliest and smallest lesions were micro-

scopic In these the epithelium of the tips of the villi had undergone hyaline fibrinoid necrosis, and a few leukocytes were present in the tissue about the necrotic epithelium In larger and presumably slightly older lesions, the necrotic material had been thrown off, resulting in erosions and superficial ulcerations, with leukocytes and fibrin at their base The lesions are believed to have been of relatively few hours' duration They were identical with those that Buchner and others of Aschoff's institute have described in the stomach as due to the action of gastric juice Their location and local character are ascribed to the course of the fluid in the duodenum after the gastric juice leaves the stomach

O T SCHULTZ

EXPERIMENTAL GASTRITIS DUE TO DILUTE HYDROCHLORIC ACID E
GOTSCHLICH, Beitr z path Anat u z allg Path **84** 632, 1930

In order to reproduce the acute lesions of the human stomach that Aschoff and his pupils have ascribed to the caustic action of the gastric juice, Gotschlich introduced by stomach tube from 15 to 20 cc of from 0.8 to 1.5 per cent of hydrochloric acid into the empty stomachs of cats In acute experiments, in which the animals were killed after from six to twelve hours, no food was given after the administration of the acid In experiments of longer duration food was permitted from eight to ten hours after the administration of the acid The pyloric portion of the stomach of cats that had received acid was found to be firmly contracted when the animals were killed, and the mucosa of this portion of the stomach was free from lesions The lesions were situated in the mucosa proximal to the pyloric region They were multiple, and were circumscribed and localized rather than diffuse They were limited to the crests of the rugae of the mucosa The smallest and earliest lesions were microscopic in size and presented the change described by the Aschoff school as characteristic of the local caustic action of gastric juice The epithelium at the tips of the villi was necrotic and glassy, and stained deeply with eosin The necroses were sometimes of a hemorrhagic character, a fact which is submitted as evidence to controvert the statement that the presence of hemorrhage is proof of the vascular origin of gastric erosions In lesions of slightly longer duration, the necrotic material was cast off The floors and sides of the erosions and superficial ulcers thus formed were infiltrated by leukocytes and contained fibrin The inflammatory reaction is secondary to the caustic action of the acid Evidences of repair of the lesions were noted early, within from eight to thirty-six hours after administration of the acid The changes noted in the healing lesions were identical with those that Konjetzky and Puhl have described in the surgically resected human stomach as the lesions of an exogenous gastritis which they hold responsible for gastric ulcer The healing lesions are not specific The acute lesions are specific and characteristic of the action of the acid of the gastric juice This initial stage was not seen by Konjetzky and Puhl in their material because it is of short duration and is transformed into the healing lesion by the preoperative treatment to which patients are subjected

O T SCHULTZ

A SPONTANEOUS PARARENAL HEMATOMA IN ACUTE MYELOID LEUKEMIA A
GÁL, Centralbl f allg Path u path Anat **49** 33, 1930

A huge right pararenal hematoma was found in the body of a 47 year old man dying from myeloid leukemia It was apparently of extrarenal origin, extended through the fatty capsule, and was in contact with collections of blood in muscles altered by myeloid infiltrations Such hematomas occur only once in the course of disease of the kidney as against eleven times from extrarenal sources The extrarenal causes are trauma, hemophilia and hemorrhage in the course of sepsis or of such diseases as scarlet fever or leukemia

GEORGE RUASTINAT

ATHEROSCLEROSIS IN PARROTS M HESSE and K WALKOFF, Centralbl f allg Path u path Anat **49** 40, 1930

The arteries of two parrots, one 48 years old and the other 60 years old, were altered by fatty and hyaline regions as in typical atherosclerosis seen in senile human beings or in guinea-pigs fed diets rich in fat Age seems to be a factor in bringing about these changes in parrots, although similar changes are not seen in birds kept on natural diets in zoological gardens

GEORGE RUKSTINAT

TWO UNUSUAL CYSTS OF THE THYROID GLAND R BAYER, Centralbl f allg Path u path Anat **49** 137, 1930

The two cysts described occurred in an unusual position, namely, below the hyoid bone Most of these cysts are found near the base of the tongue The difference in age between the persons from whose bodies the cysts were obtained was also noteworthy, one cyst was found in an 8 weeks old boy, and one in a 78 year old woman

GEORGE RUKSTINAT

A SPONTANEOUSLY HEALED DISSECTING ANEURYSM OF THE AORTA M PLONSKIER, Centralbl f allg Path u path Anat **49** 161, 1930

In the body of a woman, 55 years old, who had suffered from cardiac weakness for several years, a dissecting aneurysm extended from 3 cm distal to the right renal artery to the bifurcation of the left common iliac artery It involved the aortic wall in front for 8 by 4.5 by 4 cm and the iliac artery for 8 by 3 by 2 cm The lining of the wall of the aneurysm was smooth and resembled intima The original proximal opening into the aneurysmal space was healed, but there was still a minute opening distally into the lumen of the left common iliac artery

GEORGE RUKSTINAT

SYPHILIS OF THE PULMONARY ARTERY T REEKE, Centralbl f allg Path u path Anat **49** 257, 1930

In the body of a woman, 50 years old, dying of cardiac decompensation, a syphilitic aneurysm of the right ventricle and syphilitic mesarteritis of both the pulmonary artery and the aorta was found There was a widening of the commissure between the pulmonic leaflets In 1928, the Wassermann reaction of the blood was +++ and in 1929, ++, and blood removed from the body post mortem gave a negative reaction, whereas pericardial fluid gave a positive reaction

GEORGE RUKSTINAT

THE NUMBER OF BASOPHIL CELLS IN THE HUMAN HYPOPHYSIS IN AMYLOIDOSIS OF THE KIDNEYS AND SUPRARENAL GLANDS H LITTE, Frankfurt Ztschr f Path **40** 124, 1930

Contrary to the observations of others, the author reports that the basophil cells in the anterior lobe of the hypophysis in eighteen cases of amyloidosis of the kidneys have neither decreased nor increased in number Because the majority of the suprarenal glands in these eighteen cases also showed amyloid, the question is raised whether the amyloidosis of the suprarenal glands alone may lead to an increase in the number of the basophil cells in the hypophysis, and amyloidosis of the kidneys alone to a decrease in the number of the cells If so, amyloidosis of both organs would yield about the normal number of basophil cells No relation could be demonstrated between the basophil content of the anterior lobe of the hypophysis and amyloidosis of other organs

O SAPHIR

PRIMARY LYMPHOGRANULOMA (HODGKIN'S DISEASE) OF THE INTESTINES P HEILMANN, Frankfurt Ztschr f Path **40** 151, 1930

The tumor described in this paper was removed from a woman 50 years old The tumor was located in the cecum in the region of the mesenteric attachment,

and measured 3 by 6 by 8 cm. On section the tumor was grayish white, presented a moist surface and was easily movable. In the mucosa of the colon close to this tumor, a round ulcer was noted, which measured 3 by 3.2 cm. Surrounding the tumor, the muscular coat of the intestine was distinctly hypertrophic. In the ileocecal region, enlarged lymph nodes were present, which were of firm consistency and which showed, on section, yellowish-white, well demarcated areas of necrosis. Microscopically, the lymph nodes contained many fibroblasts, endothelial cells, large and small round cells, eosinophil leukocytes and many Dorothy Reed cells. No bacteria could be demonstrated in the sections.

O. SAPHIR

THE SIGNIFICANCE OF THE ARGENTAFFINE CELLS. G. EROS, Frankfurt Ztschr f Path **40** 155, 1930

The author studies the influence of insulin, epinephrine, extirpation of the pancreas and thyroid gland and partial removal of the suprarenal glands on the number of argentaffine cells of the intestines. After injection of 10 units of insulin per kilogram of body weight into dogs over a period of one week (chronic insulin effect), the argentaffine cells increased markedly in number. The dogs were fed with a mixed diet. One dog was treated by injection of 30 mg of epinephrine over a period of eight hours. The argentaffine cells were increased in number. To another dog, 30 mg of epinephrine was given over a period of one week. The argentaffine cells showed a decrease in number. The pancreas of a cat fed with a mixed diet, was extirpated. Four days after operation, the cat was killed. The argentaffine cells were found to have increased in number. In a number of dogs and rabbits the suprarenal glands were cauterized. When the animals were kept alive longer than seven days, the argentaffine cells were found to be much more numerous than in normal animals. In one rabbit the thyroid gland was removed. The rabbit survived the operation thirty days. The argentaffine cells were more numerous than was normal. In starved animals the argentaffine cells at first seemed to have increased in number, but later disappeared. A rabbit that was kept at a temperature of 2 C showed more argentaffine cells in the intestinal mucosa than a normal rabbit. The author concludes that in animals in which the blood sugar content has been lowered, the argentaffine cells at first decrease, but later increase in number. In animals in which the blood sugar content has been increased, the argentaffine cells at first increase, but later decrease in number.

O. SAPHIR

CHRONIC THROMBOSIS OF THE PULMONARY ARTERY AND ITS MAIN BRANCHES. L. DESCLIN, Frankfurt Ztschr f Path **40** 161, 1930

The author describes two cases in which the main pulmonary artery, and six cases in which the main branches of the pulmonary artery, were partially or completely occluded by thrombi. The origin of these thrombi is traced back with great probability to a primary embolus and secondary thrombosis.

O. SAPHIR

LYMPHOID LEUKEMIA WITHOUT INVOLVEMENT OF LYMPH NODES. R. ROSSLE, Virchows Arch f path Anat **275** 310, 1930

Rossle presents two cases of chronic lymphoid leukemia in which the usual and characteristic hyperplasia of the lymph nodes was absent. In the first patient, a man aged 85, the duration of the abnormal state of the blood was not known. The leukocyte count was 97,500, with 70 per cent lymphocytes. None of the lymph nodes was enlarged. On microscopic examination the nodes did not appear hyperplastic. The spleen weighed 220 Gm, and was completely transformed into tissue composed only of small lymphocytes. Pulp cells and sinusoids could not be recognized. Moderate lymphoid hyperplasia was present in the bone marrow. The second case receives fuller discussion because of its rarity. The patient, a woman, aged 61, had been under observation for many years, having been first

seen at the age of 35, for a lesion of the leg that had recurred each winter for the previous ten years. The lesion was at first considered mycosis fungoides or premycotic erythrodermia, but in the course of time the typical blood picture of lymphoid leukemia developed, and the condition of the skin was held to be leukenaria cutis. Necropsy yielded no gross or microscopic evidence of lymphoid hyperplasia of the lymph nodes, spleen or bone marrow. Sections of the skin from various parts of the body revealed a layer of cellular lymphadenoid tissue beneath the epidermis. The tissue was composed of reticulo-endothelial cells and small lymphocytes, supported by a reticulum like that of lymphoid tissue. Rossle believes that the lymphocytes of the skin and circulating blood arose locally in the skin from reticulo-endothelial cells, and that the transformation occurred without an intervening lymphoblast stage. He considers the case a unique one of leukemia or lymphadenaria cutis, because the lymphoid hyperplasia was limited to the skin. In neither of the cases described was there leukemic infiltration of the internal organs.

O T SCHULTZ

FETAL ERYTHROLEUKOBLASTOSIS E VON GIERKE, Vichows Arch f path Anat **275** 330, 1930

The basis of von Gierke's report is a female child, born at full term, that died one hour after birth. Seven years previously he had examined postmortem a female child of the same parents, that died fifty hours after birth. That child revealed marked erythroblastosis, without edema. The parents were healthy, it is especially noted that both were free from syphilis. The infant that is the subject of the present report died as the result of intraperitoneal hemorrhage from a ruptured spleen. The latter organ weighed 112 Gm and extended beyond the midline of the abdomen and below the level of the umbilicus. Blood smears contained an abnormally large number of erythroblasts, chiefly normoblasts, and of leukoblasts, identified as myeloblasts and neutrophil and eosinophil myelocytes. The liver, spleen and kidneys contained numerous focal areas of erythroblastic and leukoblastic tissue. The liver cells were laden with hemosiderin and iron-free pigment. The blood contained the pigment xanthorubin, previously detected only in hepatectomized dogs. Its presence is interpreted by von Gierke as evidence of severe damage to the liver. There was no edema. Fetal erythroblastosis is frequently associated with generalized anasarca of the fetus and with an abnormally large placenta. Fetal erythroblastosis has been held to be fetal anemia, to which the edema is secondary. Von Gierke points out that edema may be absent, as in his two cases, and that when present, it has usually been in stillborn or moribund infants. He considers the condition as it existed in the second child more closely related to leukemia than to anemia. Because of the lability and multiple potencies of the fetal hematopoietic system, the unknown stimulus to proliferation of leukoblastic tissue may also act on the erythroblastic tissue, sometimes to a greater degree than on the leukoblastic tissue. The condition is a systemic disease of the hematopoietic tissues. It is associated with a disturbance of hemoglobin metabolism, which manifests itself by jaundice and by the deposition of iron-free and iron-containing pigment in the tissues. In his first case there was marked "Kern" icterus of the basal ganglions of the brain.

O T SCHULTZ

Pathologic Chemistry and Physics

SERUM-CALCIUM IN PNEUMONOCONIOSIS MARTIN J SOKOLOFF and A CANTAROW, Am Rev Tuberc **22** 449, 1930

In a group of thirty patients with pneumoconiosis, fifteen of whom had an associated active tuberculous lesion, the serum-calcium ranged from 7.98 to 14.81 mg per one hundred cubic centimeters, being above normal in twenty-six patients, subnormal in one and normal in three. The serum-calcium level bore no relation to the incidence or activity of the complicating tuberculous process.

The hypercalcemia in pneumoconiosis is in all likelihood dependent on the increase in the carbon-dioxide tension of the blood, which is an inevitable consequence of the pulmonary lesion

H J CORPER

THE INORGANIC PHOSPHORUS OF THE BLOOD IN RICKETS A F HESS, MILDRED WEINSTOCK, H RIVKIN and J GROSS, J Biol Chem **87** 37, 1930

The decrease in the inorganic phosphorus of the blood, which is often associated with rickets, does not appear to be an essential or inherent feature in the pathogenesis or in the healing of the disease. If calcium or phosphorus in a favorable ratio, as in milk, are included in a rachitogenic diet, the addition of small amounts of viosterol to the diet may be followed by an increase in the inorganic phosphorus without healing of the rachitic lesions. The addition of larger amounts of viosterol is followed by prevention and healing. The addition of cod liver oil to the diet is followed by definite healing, although the phosphorus value attained is not high. A local disturbance at the epiphyses may prevent the anchorage of calcium and phosphorus in the cartilage of the bones

E R MAIN

LIPIDS IN XANTHOMA H C ECKSTEIN and U J WILE, J Biol Chem **87** 311, 1930

Tumor fat appears to have a higher iodine value and to contain a larger proportion of the more highly unsaturated fatty acids than normal human subcutaneous fat or the fat adhering to tumors. The total lipids of the tumor fat contain 48.81 per cent of cholesterol and 8.1 per cent of phospholipid, concentrations that are 200 times in excess of those found in normal fat. The nature of the lipids in xanthomas appears to be more dependent on the activity of the tissue than on the nature of the lipids present in the blood

E R MAIN

A CRYSTALLINE DERIVATIVE OF AN ACID IN THE LIVER IN PERNICIOUS ANEMIA RANDOLPH WEST and MARION HOWE, J Biol Chem **88** 427, 1930

A crystalline salt of an acid which is effective in producing the remission of pernicious anemia has been isolated from a highly purified preparation of liver extract. Analyses indicate that the acid may be β -hydroxy-glutamic acid

E R MAIN

THE COPPER CONTENT OF INFANT LIVERS D B MORRISON and T P NASH, JR, J Biol Chem **88** 479, 1930

The average content of copper in the livers of infants is 24 mg per kilogram of fresh tissue, about six times that of the livers of adults

E R MAIN

CHEMICAL ALTERATIONS IN THE BLOOD OF RATS INFECTED WITH TRYPANOSOMES R W LINTON, J Exper Med **52** 695, 1930

Samples of blood from rats infected with *Trypanosoma lewisi* give normal values for lipid phosphorus, lecithin, carbon dioxide-combining capacity, and liver glycogen. When these results are compared with the results of similar experiments with *T. equiperdum* infections, on the basis of concentration of trypanosomes in the blood, it is found that the pathogenicity of the latter organism does not depend on its numbers as affecting the blood, but that it must be in some other way injurious to the host. Whether the injury is due to a true toxin, an endotoxin, or mechanical interference is not yet known

AUTHOR'S SUMMARY

COPPER CONTENT OF HUMAN ORGANS H KLEINMANN and J KLINKE, *Virchows Arch f path Anat* **275** 422, 1930

The role ascribed by Mallory to chronic intoxication by copper in the etiology of hemochromatosis has led to the development of new methods for the quantitative estimation of minute amounts of copper in the tissues. The authors modified slightly the colorimetric method of Schonheimer and Oshima. They give in detail the technical procedure used by themselves. The average error of the method in control blank analyses was 17 per cent, and in control analyses of tissues to which known amounts of copper had been added the error was 3.6 to 6.8 per cent. Their results are tabulated as milligrams of copper per kilogram of dried substance in the case of organs examined and as milligrams of copper per liter in the case of blood. The copper content of twelve normal adult livers varied from 11.8 to 487 mg, with an average of 27.5 mg. These figures are slightly higher than those of Schonheimer and Oshima. Two samples of blood contained, respectively, 17 and 14 mg of copper. A sample of cardiac muscle contained 22 mg, and one of skeletal muscle, but from another and younger person, contained 18 mg of copper. The copper content of the liver in a typical case of hemochromatosis was 133 mg, a decided increase above the normal average. The liver in another case considered hemochromatosis, but with the pigmentary changes limited chiefly to the intestine, contained 183 mg of copper. Two livers with nonpigmented cirrhosis contained, respectively, 87 and 39 mg of copper. Of greatest interest are the relatively large amounts of copper found in the livers of fetuses and new-born infants. The copper content of ten such livers varied from 137.5 to 450 mg, with an average of 303 mg. The copper content of livers of three children, aged, respectively, 13 weeks, 14 months and 2 years, varied from 12 to 26 mg. The thoroughly transfused liver of a new-born infant contained 516 mg of copper, proving that the high copper content of the liver at this period of life is not due to the copper of the blood in the organ. The large amount of copper in the liver of the fetus and of the new-born infant is interpreted as evidence of the important functional role of this element in the normal physiology of the fetus and of the very young infant.

O T SCHULTZ

THE EFFECT OF PITUITARY ON THE IONIC OUTPUT IN THE URINE T POULSSON, *Ztschr f d ges exper Med* **72** 232, 1930

Following intramuscular injections of pituitary, in doses of from 10 to 15 units, characteristic changes in the ionic content of the urine were noted. The amount of total fixed base in proportion to the amount of sodium was increased. There was a decrease in the ammonia fraction, although the actual reaction of the urine was more alkaline.

PEARL ZEEK

BLOOD CHEMISTRY IN PUERPERAL INFECTION E O GAESSLER, *Ztschr f d ges exper Med* **72** 726, 1930

Successive determinations of the alkali reserve, blood sugar and lactic acid in the blood during the various stages of puerperal infection revealed characteristic values, which facilitate a differential diagnosis, besides being of value to prognosis and therapeutics.

PEARL ZEEK

Microbiology and Parasitology

CHRONIC EPIDEMIC ENCEPHALITIS W B STEWART and M J EVANS, *Am J M Sc* **180** 256, 1930

The Pfeiffer bacillus was isolated from all the nasopharyngeal cultures from 165 patients with chronic encephalitis. The serums from these patients agglutinated the Hammett strain of this bacillus. Of the control series, 46 per cent of naso-

pharyngeal cultures were positive for the Pfeiffer bacillus, but of 122 nonencephalitic serums, 114 neither agglutinated nor flocculated this bacillus. Of 20 cases of chronic encephalitic Parkinsonism studied for sinus disease, 18 gave positive results either by roentgen or clinical examination, 13 of these had definite disease of the ethmoids. Of 46 patients with chronic encephalitic Parkinson's disease treated for one month or more with the soluble antigen, 78 per cent showed improvement. This was not considered as due to a nonspecific protein reaction, because the amount of protein involved was so small.

JOHN PHAIR

TISSUE REACTIONS IN RABBITS FOLLOWING INTRAVENOUS INJECTION OF BACTERIA R. N. NYE and F. PARKER, JR., *Am J Path* 6 381, 1930

Following the intravenous injection into rabbits of relatively large doses of various dead bacteria, there is a marked reaction of the tissues that contain cells of the reticulo-endothelial system. This reaction consists in an increase of lymphoid cells, which are eventually transformed into, or replaced by, monocytes and giant cells. Such lesions ordinarily are temporary and result in no permanent damage. Identical lesions occur after the intravenous injection into rabbits of various colloidal substances. Such changes represent the reaction of normal rabbits in the disposition of foreign materials in the blood stream and have nothing to do with reactions secondary to sensitization or immunization.

AUTHORS' SUMMARY

A BACTERIOLOGICAL AND CLINICAL STUDY OF GASTRIC ULCER E. WATTS SAUNDERS, *Ann Surg* 92 222, 1930

On the basis of bacteriologic work, the infectious theory of gastric ulcer is supported, rather than the vascular, toxic, neurologic or chemical explanations, because of the following observations. A streptococcus was isolated from nineteen resected gastric or duodenal ulcers. This organism proved to be identical and specific by differential culture tests, agglutination, cross-agglutination and agglutinin absorption. Its agglutinogenic and antigenic identity with similar strains producing ulcers of mucous membranes and skin was demonstrated, and likewise its non-identity with strains from foci of infection, appendicitis and cholecystitis was shown. In 100 per cent of the cases tested there were specific agglutinins in the blood serum, whereas these did not occur in other types of streptococcus infections. It is suggested that the marked formation of lactic acid by this organism may have some relation to carcinomatous degeneration.

RICHARD A. LIFVENDAILL

TRACHOMA AND AVITAMINOSIS A. I. KLINDALL and S. R. GIFFORD, *Arch Ophth* 4 322, 1930

The authors report experiments designed to test the effects of vitamin A deficiency per se as a predisposing factor to infection with *Bacillus granulosus*. White rats were used and cultures of *Bact granulosus*. Fresh trachomatous material was inoculated. Three series of rats were tested as follows: rats deprived of vitamin A for thirty days and exhibiting keratomalacia before inoculation, rats deprived of vitamin A for ten days before inoculation, and rats deprived of vitamin A for ten days, then inoculated, first with cultures of *Bact granulosus* previously grown on rat-blood agar, and finally with cultures grown on Noguchi's leptospiral medium. Series 2 and 3 were kept on a vitamin-A-free diet for an additional eighteen days. No changes were seen in the eyes of the animals, even when inoculations of *Bact granulosus* were preceded by injections of *Bacillus pseudotuberculosis*, *rodentium*, streptococci, etc., which caused a transitory inflammation.

"It must be admitted that the white rat may have a degree of resistance to the trachoma virus that transcends even the effects of a prolonged starvation of vitamin A."

Negative results attended the instillation of fresh trachoma material (from which *Bact granulosis* was isolated) into the eyes of white rats thoroughly deprived of vitamin A. "In the light of the statements that dogs, cats and monkeys may spontaneously contract folliculosis, it would appear that the lack of success in inducing even a transitory reaction with fresh trachoma material after deprivation of vitamin A is suggestive that such deprivation per se is not necessarily a factor in trachoma infection. This, however, is not to be construed as an argument against the statement that deprivation of vitamin A is a contributory cause."

CHARLES WEISS

EXPERIMENTAL SYPHILIS G. C. LAKE and K. K. BRYANT, Bull Nat Inst Health, 157, 1930

The lymph gland transfer method for the determination of the presence of the *Treponema pallidum* in human cases of syphilis was applied in sixty-six instances. The group included thirty-four early cases in untreated patients, fifteen early cases in partially treated patients, nine old cases (average duration 69 years, in insufficiently treated patients, and eight old cases (average duration 225 years) in untreated patients. We were able to demonstrate the spirochete in the testicles of rabbits inoculated with emulsified lymph glands from each of the thirty-four untreated patients with early syphilis and from four of the nine insufficiently treated patients with old syphilis. All of the other transfers yielded negative results, even after subculture to a second group of animals. The results obtained indicate the impracticability of using the intratesticular injection of emulsions of human lymph glands into rabbits as a method for determining the presence or absence of syphilis in man, except in the early stages in untreated patients. Similarly our work shows the impracticability of applying this method to the measurement of the chemotherapeutic activity of the arsenicals in the treatment of patients with syphilis.

Our experience has shown us the value of using the results of two sensitive serologic tests as presumptive evidence of syphilis in rabbits and as indicating the degree of probability of being able to demonstrate the spirochete by the dark field examination of testicular puncture material from rabbits inoculated by the technic that we have employed. It has also shown us the value of the dark field examination of emulsion of the entire testicle into which injection was made as the final test for the presence of *T. pallidum*, particularly in the case of an "asymptomatic" animal.

The results which we obtained in the production of syphilis in the rabbit indicate that if careful clinical examinations are frequently made of the original group of inoculated animals, if sensitive and dependable serologic tests are employed, and if final dark field examinations are made of an emulsion of the entire inoculated testicle from each rabbit, subsequent subculturing of the negative animals into a second group of rabbits will not significantly increase the number of positive observations. The additional time and expense involved outweigh the results to be expected.

AUTHORS' SUMMARY

BRUCELLA IN STOOLS AND BILE H. L. AMOSS and MARY A. POSTON, J. A. M. A. 95 482, 1930

Brucella has been isolated seventy-eight times from the stools of six patients. The use of liver agar as the basis for the eosin-methylene blue plates offers no improvement over the use of meat extract agar. *Brucella* has been obtained in cultures from the bile procured by duodenal drainage and from the contents of the gallbladder at operation in a case of chronic *Brucella* infection. The causative organisms may not always be present in the stools in acute cases of *Brucella* infection.

PSITTACOSIS J M RIVERS, G P BERRY and C R RHODES, J A M A
95 579, 1930

The virus of psittacosis is in the feces and in the material collected from the nose, mouth and procrop of infected parrots. Parrots and monkeys can be infected by intranasal instillations of the virus. Parrots and rabbits that have recovered from a primary infection are refractory to reinfection. It is not a simple matter to demonstrate neutralizing properties in convalescent human serum. In parrots and in mice, the principal lesions occur in the liver and spleen. Young monkeys (*Macacus rhesus*) are susceptible to intracerebral, intra-tracheal and intranasal inoculations of psittacosis virus. When it is instilled into the nose or injected into the trachea a characteristic pathologic picture occurs in the lungs which is similar to that observed in man.

AUTHORS' SUMMARY

STREPTOCOCCAL INFECTIONS OF EPIPHYSES AND SHORT BONES D B
PHEMISTER, A BRUNSCHWIG and L DAY, J A M A 95 995, 1930

Bacteriologic studies were made of biopsy material in two cases each of Kohler's disease of the tarsal scaphoid, Legg-Perthes' disease and Kienboch's malacia of the os lunatum. Streptococci grew in cultures in four of the cases, cultures in two remained sterile. A streptococcus that on blood agar plates was more hemolyzing than green-producing and on dextrose blood agar plates more green-producing than hemolyzing grew in cultures in one case of Kohler's disease showing acute symptoms. Green-producing streptococci grew in cultures in one case of Legg-Perthes' disease and in one case of Kienboch's malacia. A streptococcus that was not further identified grew in cultures in one case of Kienboch's malacia. One case of Kohler's disease in which the cultures and the results of guinea-pig inoculations were negative occurred in association with multiple osseous and lymph-glandular tuberculosis. One apparent case of Kohler's disease developed following traumatism. These observations suggest that streptococci play an important rôle in the etiology of these diseases, but that other factors may also bring them about. Whether the streptococci reach the bone in an embolus which blocks the main artery or whether they lodge there alone remains undetermined.

AUTHORS' SUMMARY

RELATIONSHIP OF THE SCROTAL SWELLING AND RICKETTSIA BODIES TO
MEXICAN TYPHUS FEVER M RUIZ CASTANEDA, J Exper Med 52 195,
1930

Scrotal swelling can appear in guinea-pigs directly inoculated from a human case of Mexican typhus fever. With certain strains of this disease, a number of generations of guinea-pigs may show absolutely no scrotal swelling, which, however, may reappear in subsequent animals, suggesting, though not absolutely proving, that the scrotal swelling is an integral part of the disease and is not due to an incidental accompanying organism. If the latter were true, one would expect the organisms that caused the scrotal swelling to disappear during the negative generations. A typhus fever sustained by a guinea-pig without scrotal swelling protects against the swelling on subsequent inoculation with a strain that produces this with considerable regularity. Passage through lice increases the capacity of a strain to produce the scrotal lesion, probably because of the considerable accumulation of rickettsia in the louse, but in the experiment noted, even with a strain that had been passed through lice, absence of swelling for two generations occurred, followed by recurrence of the swelling.

AUTHOR'S SUMMARY

SUSCEPTIBILITY OF RABBITS TO INFECTION BY THE INHALATION OF TYPE II PNEUMOCOCCI ERNEST G STILLMAN, J Exper Med **52** 215, 1930

The susceptibility of rabbits to infection by inhalation of *Pneumococcus* varies in direct proportion to the virulence of the organism for rabbits. When rabbits are exposed to a pneumococcus spray, irrespective of the virulence of the organism, the bacteria readily penetrate into the lower part of the respiratory tract. When rabbits are exposed to a spray of the avirulent, degenerated "R" form of *Pneumococcus*, septicemia does not occur, and pneumococci are seldom recovered from the liver, kidney or spleen. When rabbits are exposed to a spray of slightly virulent *Pneumococcus* Type II (SAv), a nonfatal septicemia may occur, and pneumococci may be recovered from the liver, kidney and spleen. When rabbits are exposed to a spray of virulent Type II (Sv) pneumococci, septicemia may occur which in certain instances terminates fatally. Pneumococci may also be recovered from the liver, kidney and spleen.

AUTHOR'S SUMMARY

SURVIVAL AND MULTIPLICATION OF THE VIRUS OF POLIOMYELITIS IN VITRO P H LONG, P K OLITSKY and C P RHOADS, J Exper Med **52** 361, 1930

The study here reported concerns attempts at bacteriologic cultivations with fragments of brain or cord, or with Berkefeld V filtrates of the nervous tissues, from seven monkeys successfully inoculated with poliomyelitic virus. With these materials, 315 tubes were inoculated, of which 36 showed minute bodies resembling the globoid bodies described by Flexner and Noguchi. However, a study of subplants from these minute, morphologic particles did not convince us that we had in hand actual cultures of the globoid bodies, or indeed of any living micro-organism. Nevertheless, when washed sediments from subplants of one of the strains, representing the seventh, eighth, ninth and tenth transfers, were inoculated into monkeys, the clinical signs and pathologic effects characteristic of experimental poliomyelitis were induced. The virulence of the "cultures" could not be ascribed to carrying over the origin material into these remote subplants since the seventh transfer represented a dilution of the original cultivated material to about 15×10^{-12} , and the tenth, to about 13×10^{-18} , if one assumes, as the transfer technic justifies, a thorough mixing of the contents of each tube. On the contrary, it appears as if the poliomyelitic virus had multiplied in vitro, and had increased as a consequence of being in a medium of a modified living tissue-cell culture. For in practically all specimens we observed many well preserved kidney tissue cells and leukocytes, the latter probably derived from human ascitic fluid, a component of the Smith-Noguchi medium. In this connection, it should be mentioned that the several lots of ascitic fluid used in the cultivation tests were recently obtained from patients and employed for from a week to a month after their collection. There remains for consideration the problem of the selective pathogenicity of the "cultures" only the material of those tubes of the ninth and tenth transfers which showed the "globoid bodies" proved pathogenic, those respective tubes of the same transfers which were free from the minute bodies, but apparently identical in all other respects, were avirulent. It may be that the virus was adsorbed to the particular bodies that we have found in the "cultures" and that resemble closely the globoid bodies of Flexner and Noguchi. Further elaboration of this study would be necessary, however, before such an inference could be regarded as a definite hypothesis.

AUTHORS' SUMMARY

CULTIVATION OF VACCINE VIRUS C P LI and T M RIVERS, J Exper Med. **52** 465, 1930

A strain of neurovaccine virus was cultivated in a medium consisting of minced chick embryo suspended in Tyrode's solution. The virus on cultivation apparently lost none of its essential characteristics. The culture virus can be preserved and stored for long periods of time. Furthermore, the preserved virus can be used to initiate fresh cultures.

AUTHORS' SUMMARY

HOST FACTORS IN THE PATHOGENESIS OF PNEUMOCOCCUS PNEUMONIA EZRA
A SHARP and FRANCIS G BLAKE, J Exper Med 52 501, 1930

The present study was undertaken in order to determine whether animals exhibiting cutaneous hypersensitiveness to pneumococcus would show an acute inflammatory reaction in the lungs when pneumococcus autolysate was brought into contact with the pulmonary tissues, and, if so, whether the pulmonary reaction might be shown to be due to the allergic state of the animal, rather than to intrinsic properties of the autolysate. Twenty young rabbits were sensitized to pneumococcus by various procedures, and their degree of hypersensitiveness was determined at frequent intervals over varying periods of time by means of intracutaneous injections of pneumococcus autolysate standardized on the basis of nitrogen content and so treated as to be devoid of the known toxic principles. Twenty-four hours after the last skin test, each rabbit was given an intratracheal injection of the same pneumococcus autolysate. Seven nonsensitive controls were given similar injections intratracheally. Twenty-four hours after the intratracheal injection, the rabbits were killed. The lungs were removed, a portion was cultured, and the rest was examined histologically. Of the twenty sensitized rabbits, three that showed no cutaneous sensitivity and three that were only slightly skin-sensitive at the time of intratracheal injection exhibited no detectable pulmonary reaction to the autolysate, eleven of fourteen that showed moderate to extreme cutaneous hypersensitiveness were found to have an acute exudative inflammation of the lungs. The exudate consisted largely of polymorphonuclear leukocytes and serum. It varied in extent from a slight focal exudate lining the bronchioles and adjacent alveoli to a marked diffuse involvement of considerable portions of the lung. In all but one of the eleven cases the cultures of the lungs were sterile. The single animal yielding a positive culture (*Bacterium leptosepticum*) has been excluded. None of the seven nonsensitive controls showed any pulmonary reaction to the autolysate. From these results it may be concluded that there is in rabbits a fairly close parallelism between cutaneous and pulmonary hypersensitiveness to pneumococcus autolysate, and that the inflammatory response of the pulmonary tissue resulting from contact with the autolysate depends on the allergic state of the animal rather than on inherently injurious substances in the autolysate. The observations are in harmony with the theory that allergy may play a part in the pathogenesis of pneumococcus pneumonia in man.

AUTHORS' SUMMARY

THE DISTRIBUTION OF FRIEDLANDER'S BACILLI OF DIFFERENT TYPES LOUIS
A JULIANEIL, J Exper Med 52 539, 1930

In a study of the distribution of the specific types of Friedlander's bacillus, it is shown that, of eighty strains, 52 per cent belong to type A, 15 per cent to type B, 9 per cent to type C and 24 per cent to group X. Type A includes for the most part strains derived from diseases of man, and more than 70 per cent are associated with pneumonia in man. Type B includes the greatest number of strains from animal sources, while the heterogeneous strains comprising group X come from the greatest variety of diseases. It was demonstrated that in a patient with pneumonia due to Friedlander's bacillus (type A) a specific precipitin reaction of the urine occurred in the corresponding (type A) immune serum. A study of the sugar fermentations of Friedlander's bacillus shows that there is no correlation between serologic type and fermentative activity, the fermentation reactions are variable and therefore not reliable for distinguishing Friedlander's bacillus from closely allied organisms, the strains of group X show the greatest variation in fermentation, and of fifteen strains unable to ferment lactose, thirteen belong to type A.

AUTHOR'S SUMMARY

EXPERIMENTS ON T. LEWISI INFECTION IN ALBINO RATS DAVID PERLA and
J MARMORSTON-GOTTESMAN, J Exper Med 52 601, 1930

Trypanosoma lewisi infection was studied in normal rats by daily quantitative estimates of the trypanosomes in the blood during the course of the infection.

Splenectomized rats, after *T. lewisi* infection, showed an increased mortality of from 30 to 100 per cent due to *Bartonella muris* anemia. This was at the height of the anemia, seven days after splenectomy. After forty-eight days, when the anemia had disappeared, *T. lewisi* infection was more severe than in normal rats. Splenic autotransplantation four weeks prior to splenectomy raised the resistance to subsequent *T. lewisi* infections. Thymectomy shortened the course and lessened the severity of the infection. Bilateral gonadectomy in the adult increased the severity of the infection, and the number of trypansomes at the height of infection was greatly increased. Unilateral gonadectomy did not influence the infection.

E. DELVES

BACTERIUM GRANULOSIS IN RELATION TO TRACHOMA E. B. TILDEN and J. R. TYLER, J. Exper. Med. **52** 617, 1930

The original culture of Noguchi (Albuquerque 1), after 2½ years of growth on artificial medium, gave positive results on inoculation in about one third of a total of 15 rhesus monkeys. The lesions, however, were not progressive and often receded after a few months. Two chimpanzees similarly infected showed only a few follicles which did not progress. Rhesus monkeys immunized by subcutaneous or intravenous injection of *Bacterium granulosis* were not protected against subconjunctival infections with emulsions obtained from active conjunctival lesions in the monkey. Transmission of this strain (Albuquerque 1) by passage from eyelid to eyelid in a series of 30 rhesus monkeys, an emulsion of conjunctival tissue being used, gave more striking results. The lesions were more severe and lasted a much longer time. With repeated passages of material from the conjunctiva of one monkey to that of another, the incubation period became longer (it rose from 13 to 139 days), and the positive results less frequent. In one experiment, a suspension made from the excised conjunctiva of a monkey (M rhesus 72) with active lesions infected only 1 of 15 monkeys. When several monkeys (4 or 5) were inoculated with a given conjunctival suspension, it was not uncommon for only one of the series to show lesions and occasionally all failed to present them. Pannus never developed. There was no entropion or ectropion. Occasionally the lesions disappeared or remained unilateral. At times monkeys showed no lesions in the inoculated eye and good lesions in the uninoculated one.

Attempts at the isolation of *Bact. granulosis* from active, untreated lesions in man or monkey did not always succeed. Similarly, the organism was not recovered from the secretions of an active infection in a monkey (M rhesus 51).

Six additional strains of *Bact. granulosis* were isolated by the authors from cases of trachoma occurring in the Indian schools of Arizona. The cultures thus obtained were identical morphologically and culturally with those isolated by Noguchi, and induced the same chronic granular conjunctivitis in monkeys. Advanced cases in which treatment had not been given were more favorable for cultural study than cases in which treatment had been begun.

Cultures of *Bact. granulosis* kept on semisolid medium containing 10 per cent rabbit serum ("leptospira medium") remained viable for many months at room temperature, and sealed ampules of such cultures were found to retain their pathogenicity for the conjunctiva of the monkey for at least 69 days at room temperature, and for at least 284 days at from 4 to 6 C.

Several additional cultural and biologic characteristics of *Bact. granulosis* are described. Of outstanding importance is the fact that cocaine, in contradistinction to procaine, had a bactericidal effect on the organism. This fact in view of the common use of cocaine for anesthesia, may explain the negative results of cultivation experiments reported by some workers.

CHARLES WEISS

FUNGI ISOLATED FROM SKIN DURING AN EPIDEMIC OF PERLECHE ERNST PRIEBRAM, J. Infect. Dis. **47** 1, 1930

In an epidemic of perleche, yeast cells were isolated from the skin lesions. Three different types were found and classified *Mycoderma*, *Candida* and

Cryptococcus These types have different characteristics *Mycodeima* has an unbranched mycelium without conidia, *Candida* has a branched mycelium and ovoid or spherical conidia, *Cryptococcus* has no mycelium and spherical or hexagonal cells without spores The three types are connected by transition forms, which may be called incomplete or imperfect forms of the *Candida* type The fermentation of lactose by the majority of the strains suggests an infection by way of milk or cream

AUTHOR'S SUMMARY

RINGWORM OF THE SCALP CAUSED BY *ALTERNARIA TENUI* NEES ERNST
PRIBRAM, J Infect Dis 47 11, 1930

A mold containing a brown pigment and brown spores has been isolated in different epidemics of ringworm of the scalp It has been identified as *Alternaria*

AUTHOR'S SUMMARY

THE TYPES OF TUBERCLE BACILLI FOUND IN TUBERCULOUS LESIONS AND IN
NONTUBERCULOUS TISSUE IN MAN J D ARONSON and C E WHITNEY,
J Infect Dis 47 30, 1930

Tubercle bacilli obtained from latent and progressive lesions and from non-tuberculous tissue fall into two distinct groups, with occasional atypical strains The human type of tubercle bacilli is characterized by luxuriant growth on glycerol agar and slight pathogenicity for the rabbit The bovine type of tubercle bacillus is characterized by sparse growth in early generations on glycerol agar and high pathogenicity for the rabbit The atypical strains may grow luxuriantly on glycerol agar and be highly pathogenic for rabbits, or the cultures may grow sparsely and be slightly pathogenic for rabbits The glycerol reaction curve was not found to be specific for the respective types No difference between the types could be detected by means of the complement-fixation reaction From latent tuberculous lesions of human autopsy material there were isolated eighty-three cultures of the human type of tubercle bacillus, three of the bovine type and two atypical strains From progressive tuberculous lesions, ninety-six cultures of the human type and three of the bovine type were isolated From lung tissue, pulmonary lymph nodes and mesenteric lymph nodes free from tuberculous lesions, there were isolated thirty-eight cultures of the human type and two atypical cultures Three of the bovine cultures were obtained from guinea-pigs inoculated with material from latent pulmonary tuberculous lesions in patients aged 42, 65 and 65 years Three cultures of bovine tubercle bacilli were obtained from the mesenteric nodes of children, aged 10 and 12 months, and from a lung of the second child The atypical strains of tubercle bacilli were isolated from two patients, aged 57 and 70 years Two of the cultures were obtained from nontuberculous lesions and two from a latent tuberculous lesion

AUTHORS' SUMMARY

THE LOCALIZATION OF STREPTOCOCCI IN THE TISSUES OF RABBITS EUGENIA
VALENTINE and MARTHA VAN METER, J Infect Dis 47 56, 1930

The results obtained in this study indicate that the localization of streptococci in the tissues of rabbits following the intravenous inoculation of unpurified mass cultures is not intimately dependent on the source of the specimen or the clinical history of the person furnishing it Regardless of the origin of the specimens, lesions were found in the joints in 65 per cent of the rabbits, in the muscles in 22 per cent, in the heart in 21 per cent and in the kidney in 18 per cent Following the injection of two culturally or serologically different varieties of *Streptococcus*, the organisms were found to localize independently in different joints or tissues, or one type was found to invade one rabbit, while the other type predominated in the other animal, or one type, preeminently the green-producing varieties, might invade to the exclusion of the other In virtually all

instances streptococci isolated from lesions of inoculated rabbits were found to be similar culturally and serologically to those isolated from the original mass culture. Little difference was noted between the invasive capacity of streptococci vegetating on the mucosa of the buccal cavity and those isolated or cultured from acute or chronic apical abscesses. The variation in the susceptibility or resistance of individual rabbits, into which injections of the same culture at the same time in approximately the same dosage were made, is so marked that it is deemed unjustifiable to draw conclusions regarding elective localization from the results obtained by the injection of less than a considerable number of animals per specimen. No evidence of localization of streptococci in the bony structure of the labyrinth of the ear was noted in 100 rabbits examined at autopsy.

AUTHORS' SUMMARY

PLEOMORPHIC MICRO-ORGANISM ASSOCIATED WITH INFECTIOUS AVIAN LARYNGOTRACHEITIS. ROBERT GRAHAM, FRANK THORP, JR., and W. A. JAMES, *J. Infect. Dis.* **47** 83 and 87, 1930

A pleomorphic micro-organism isolated from the laryngeal and tracheal exudates of fowls, naturally infected with acute infectious laryngotracheitis, is a gram-positive, hemolytic, nonmotile, nonspore-bearing, facultative anaerobe, which requires a blood agar medium for its successful cultivation. Morphologically, the pleomorphic micro-organism has coccoid, diplococcoid, ovoid, granular or beaded rod forms suggestive of the diphtheroid group. Subacute or chronic avian laryngotracheitis (a mild form of the acute disease) has been observed in flocks in which other fowls previously (from three to six months) suffered from the acute and fatal type of the disease, as well as in flocks in which a negligible number of acute cases of the disease were simultaneously recognized. The subacute type of the disease can be propagated continuously from fowl to fowl by placing a sterile cotton swab in the larynx of an infected fowl and then in the larynx of a healthy fowl. The acute form of the disease cannot be continuously transferred from fowl to fowl by laryngeal swabs. By this method of exposure, the acute type is transformed into the subacute. The subacute type, by repeated laryngeal transfers, in our experience does not become acute. The subacute or chronic type of avian laryngotracheitis has a low mortality in naturally as well as in artificially induced cases. Clinically, the disease is characterized by mild intermittent symptoms of a low grade inflammation of the larynx and trachea, which consist of shaking the head and rapid intermittent swallowing, with solitary stenotic laryngotracheal sounds or a continuous "wheezing" sound. Normal egg production, color of the comb and appetite are not necessarily altered. Dulness and lack of vigor may be periodically observed in the chronic, subacute type of the disease, followed by emaciation and death. A pleomorphic micro-organism was isolated from fowls naturally infected with the subacute type, as well as from fowls artificially infected by swabs from the acute disease. This micro-organism is pleomorphic and appears indistinguishable from the pleomorphic micro-organism encountered in the acute and fatal form of the disease.

AUTHOR'S SUMMARY

THE LENGTH OF SURVIVAL OF PARATYPHOID BACILLI IN FOODSTUFFS. L. P. DOYLE, *J. Infect. Dis.* **47** 92, 1930

The length of time for which paratyphoid bacilli lived after being introduced into certain canned vegetables varied within wide limits. *Salmonella acitrycke* remained alive in canned spinach for three years. *S. acitrycke* and *S. enteritidis* agglutinogens were easily demonstrated in unheated corn, spinach and peas three years after inoculation. *S. acitrycke* agglutinogens were clearly demonstrable in the vegetables after being heated. Relatively slight heating apparently destroyed or greatly reduced the *enteritidis* agglutinogens.

AUTHOR'S SUMMARY

PRESENT KNOWLEDGE OF THE ETIOLOGY OF TRACHOMA CHARLES WEISS,
J Infect Dis 47 107, 1930

It must not be assumed that even if *Bacterium granulosis* is finally accepted as the cause of trachoma, an end will have been made of this great problem. On the contrary, several new and promising fields of investigation will remain. For example, what is this spontaneous follicular conjunctivitis that occurs among various monkeys, chimpanzees and rabbits? What is its relation to trachoma in man? Is the presence of secretion in trachoma in man due to a mixed, a secondary bacterial or a virus infection? Are there trachoma carriers? And, of course, there will still remain the practical problem of developing specific prophylactic and therapeutic measures against this disease, which now constitutes a serious problem of public health throughout the United States and in nearly all the countries of the world.

AUTHOR'S SUMMARY

PURE CULTURES OF CLOSTRIDIUM BUTYRICUM IODOPHILUM FROM HUMAN
FECES NANNA SVARTZ, J Infect Dis 47 138, 1930

Iodophil clostridia, abundant in intestinal fermentative dyspepsia, were isolated in pure cultures from human feces. The most typical feature of these bacteria was their inclination to form and deposit starchlike, iodophil substance, and to change into clostridial form, two biologic processes that take place according to fixed rules. Comparative experiments with the strains thus isolated and those obtained from other laboratories under the names of *Bacillus amylobacter* and *Clostridium butyricum* showed that the new strains differ from the other strains. Among other tests made were those with agglutinating serum produced against one of the new strains. The comparative tests showed further that the strains of *B. amylobacter* obtained from different laboratories differed also among themselves, and that entirely different bacteria go by the same name. The name *Clostridium butyricum-iodophilum* is suggested for the iodophil clostridium-forming bacterium here described.

AUTHOR'S SUMMARY

REACTIONS IN GUINEA-PIGS FOLLOWING INOCULATION WITH HEAT-KILLED
TUBERCLE BACILLI ARNOLD BRANCH and J R CUFF, J Infect Dis 47
151, 1930

Allergy and anaphylaxis in tuberculosis are independent phenomena, and immunity may be present without allergy. Intramuscular inoculation with heat-killed tubercle bacilli (and probably also intravascular inoculation) produces immunity and anaphylaxis without allergy, whereas intraperitoneal and intrapleural inoculation produces allergy, anaphylaxis and immunity. The development of allergy appears to be interrelated with the process of caseation. The practicability of prophylactic immunization of children by intramuscular inoculation with heat-killed virulent tubercle bacilli is suggested, the advantage being that if immunity can be obtained without allergy a positive reaction in the valuable tuberculin skin test later is evidence of infection and not the result of the vaccination.

AUTHORS' SUMMARY

MENINGOCOCCUS MENINGITIS IN DETROIT, 1928-1930 JOHN F NORTON and
NORMA H BROOK, J Prev Med 4 355, 1930

During the 1928-1929 epidemic of meningitis in Detroit, sixty-two meningococcus strains were isolated from patients and thirty-three meningococcus strains from carriers (home contacts of the patients). These ninety-five strains were all agglutinated by a polyvalent antimeningococcus serum in a dilution of 1:400. In carbohydrate fermentation reactions, maltose gave the most consistent results, while saccharose fermentation was not uncommon. These cultural tests were less reliable than the serologic tests. Strains isolated from patients (spinal fluid) were, on the

whole, more virulent for white mice than those found in contact carriers (nasopharynx). Agglutination tests with serums prepared with standard group cultures gave unsatisfactory results and did not permit a definite grouping. Agglutination absorption tests showed that the organisms could be assigned definitely to group III. Both agglutination and absorption-of-agglutinin experiments with serums prepared from cases and carrier strains isolated during the outbreak in Detroit and tested against ten cases and nine carrier strains, gave definite evidence of the serologic identity of the organisms involved.

AUTHORS' SUMMARY

THE TYPE DISTRIBUTION OF MENINGOCOCCI IN THE UNITED STATES DURING 1928 AND 1929. SARA E. BRASHAM, C. E. TAIT and S. A. CARLIN, *Pub Health Rep* **45** 1131, 1930.

One hundred and fifty-five strains of meningococci, isolated during the last eighteen months, have been typed according to the classification of Gordon. Of these, 90.8 per cent fall into Gordon's four groups, whereas 9.2 per cent do not seem to be represented in that classification. Comparison with the grouping during the epidemic years 1918-1919 shows a present greater preponderance of types I and III (which are considered by many to belong to the same group), a definite decrease in type II, a marked increase in type IV, and a decrease in the number of strains that could not be typed. A striking contrast is seen in intervening non-epidemic years in which there was a great predominance of atypical strains.

These studies indicate that at least 90 per cent of the meningococci studied during this last year are typical agglutinogenically, and that they are on the whole fairly well represented in the polyvalent serums prepared for therapeutic use.

HAEMOLYSIN PRODUCED BY ANAEROBIC STRAINS OF *B. TETANI*. JOHN C. KERRIN, *Brit J Exper Path* **11** 153, 1930.

Anaerobic strains of *Bacillus tetani* secrete as powerful a hemolysin as do the toxic strains. Normal serum and cholesterol exert a powerful antagonistic effect against tetanolysin, while lecithin has no antihemolytic power.

AUTHOR'S SUMMARY

A BACTERIOLOGICAL STUDY IN THE COURSE OF CHOLECYSTECTOMY. G. G. TAYLOR and L. E. H. WHITBY, *Brit J Surg* **18** 78, 1930.

Intestinal bacteria, rather than streptococci, are regarded as the more frequent cause of infection of the gallbladder. By anaerobic methods *Bacillus welchii* was frequently found in cases of acute cholecystitis and in 9 per cent of the organs examined. The same organism was found in the centers of 13 per cent of gallstones obtained from the autopsy room. The route of invasion is most likely by way of the portal system to the liver and thence by the periportal lymphatics to the gallbladder.

RICHARD A. LIFVENDAHL

THE AETIOLOGY OF LYMPHADENOMA. C. C. TWORT, *J Path & Bact* **33** 539, 1930.

The etiology of lymphadenoma (Hodgkin's disease) remains obscure to us. We could consistently demonstrate no specific animal or vegetable parasite in the diseased tissues by direct microscopic examination, by cultivation or by injection into animals, in spite of the numerous artifices adopted. Cultures of antemortem lymphadenomatous glands were in almost all instances sterile, and we were unable to repeat the positive results which many other workers have been fortunate enough to obtain in infection experiments on animals. An assortment of other *in vivo* and *in vitro* experiments gave absolutely barren results, in fact so invariably did the different experimental procedures which we adopted lead to nothing that one

might have been dealing with a true new growth instead of what is generally accepted to be a granuloma

AUTHOR'S SUMMARY

BACTERIOPHAGE REACTIONS OF FLEXNER DYSENTERY STRAINS F M BURNET
and M McKIE, J Path & Bact **33** 637, 1930

Bacteriophages active against Flexner dysentery bacilli can be subdivided according to Bail's methods into four main groups. One of these groups comprises phages capable of lysing only the smooth phase, phages of the other three may or may not lyse smooth strains, but, with an occasional exception, lyse rough forms of all the Flexner types. Two of the latter groups are homologous with similar groups of *Salmonella* bacteriophages. The various Flexner types, V, W, X, Y, Z of Andrewes and Inman, present characteristic differences in their phage sensitivity. Antigenically similar strains show practically identical reactions toward a series of phages.

AUTHORS' SUMMARY

INFECTIOUS ECTROMELIA J MARCHAL, J Path & Bact **33** 713, 1930

A natural disease occurring in a breeding stock of mice has been described. This was characterized by high mortality in the stock and, in a minority of the sick animals, by a local lesion, usually the swelling of one hind foot, which in some mice was followed by gangrene and separation of the gangrenous portion, these mice often recovered. Animals dying without local symptoms showed, on postmortem examination, definite lesions of the liver and spleen. This disease was considered to be due to a filter-passing virus for the following reasons. Emulsions of certain organs and some body fluids proved to be infective, even in very high dilution, although there was no evidence of the presence of any bacteria. Bacteria isolated from the local lesions or internal organs did not reproduce the disease, even when large doses were given. Emulsions of the liver and spleen or other infected tissue filtered through candles (Pasteur-Chamberland L2, Mandler and Berkefeld N) capable of holding back bacteria proved to be highly infective. Histologic examination showed that the outstanding feature of the action of the virus was necrosis, which especially affected the mesoblastic tissues. Epithelial tissues, when attacked showed cytoplasmic inclusion bodies with strongly acidophil staining reactions. At low temperature, from 0 C to -10 C the virus could be preserved for long periods. Infected tissue preserved either in 50 per cent glycerin or pure glycerin and stored at 0 C remained active for months. Infected tissue dried over phosphorus pentoxide and stored at room temperature showed no loss of virus at the end of six months. At 50 C the infectivity was not entirely inactivated in two hours, at 55 C it showed complete inactivation in thirty minutes. Phenol 0.5 per cent did not inactivate it even after fifty days, phenol 1 per cent had not rendered emulsions of liver noninfective after twenty days. Formaldehyde 0.01 per cent completely inactivated the virus after forty-eight hours. An attack of the disease rendered the animal solidly immune to the injection of many lethal doses of the virus. Serum obtained from convalescent animals neutralized the effect of the virus when mixed with it before injection.

AUTHOR'S SUMMARY

INTRAOCULAR INJECTION OF VIRUS OF TSUTSUGAMUSHI DISEASE AND TYPHUS
FEVER M NAGAYO and others, Jap J Exper Med **8** 309 and 319, 1930

The virus of tsutsugamushi disease and the virus of typhus fever were inoculated separately into the eye in rabbits and guinea-pigs. In both cases, minute microbic forms were found in Descemet's membrane, and the organisms and lesions corresponded to those in patients and in otherwise infected animals. Neither virus produced changes in the eye, and no organisms were demonstrated in immune animals. Attention is called to this method for studying other viruses.

BACTERIAL HAEMOTOXIN K. NAGASE, Jap J Exper Med 8 379, 1930

After purification, the hemotoxin of *Vibrio El Tor* showed no protein reactions and contained only a small amount of nitrogen. The purified, like the nonpurified, hemotoxin produced a specific antihemotoxin. Fermentations indicate that the hemotoxin is not a protein, but may be of the nature of a carbohydrate. The streptococcus hemotoxin was found to have similar properties.

TRANSMISSION OF THE SPIROCHETES OF RECURRENT FEVER BY TICKS CHARLES NICOLL, CHARLES ANDERSON and JACQUES COLAS-BELCOUR, Arch Inst Pasteur de Tunis 19 133, 1930

An entire number of the journal, ninety-seven pages, is devoted to the compilation and orientation of published and unpublished work done since 1926 at the Pasteur Institute of Tunis on the subject of the transmission of spirochetes by ticks. Ten recurrent fever viruses and five species of *Ornithodoros*, from various sources, have been used. Following a brief discussion of the nymph stage in the life of ticks, concise experimental data are presented. The final pages of summary and general conclusions bring out these points:

Although the hosts of the spirochetes vary in their susceptibility to infection, there exists a general indifference among the ticks to the species of spirochete carried. Ticks will harbor spirochetes from regions in which previous contact, outside the laboratory, could not have occurred.

The life of the tick does not exceed twenty months when it is kept in the laboratory and fed regularly. Spirochetes may be harbored as long as from seventeen to twenty months. The males may not, in this respect, react similarly to the females.

A general rule may be stated, that the *Ornithodoros*, in the adult form, does not transmit infection by biting, but in the nymph stage does so until the adult stage is reached. There are exceptions, based on the life habits and environment of the ticks. A lapse of time is necessary after ingestion before infection is possible. The infecting stages may be maintained for five or six months—exceptionally, for fifteen months. Repeated infection of the tick does not appear to result in immunity.

Ticks infected per ovum are somewhat less constant in their capacity to infect the vertebrate host than ticks infected by ingestion. Hereditary transmission to the first generation is somewhat irregular, to the second rare and to the third never observed. This is true regardless of whether the tick-spirochete relationship is natural or foreign.

Preservation of the virus involved the factors of hereditary transmission and length of life in the ticks, and the frequency of contact with hosts suited to both tick and virus. Man is only an accidental factor in the chain.

The natural route of inoculation, ingestion, seems to afford the best opportunities for the spirochete cycle within the tick. Ticks otherwise inoculated were less frequently infected, and the virus survived a shorter time.

Although the natural vector, the tick, may be infected with spirochetes foreign to them in nature with no apparent difference in reaction, adaptation to other invertebrates of somewhat similar habits, such as lice, which might serve as vectors, is seldom successful. Conversely, adaptation to the tick of viruses normally not transmitted by the tick is seldom, if ever, accomplished.

There is danger of becoming lost in detail. Histologic studies of the ticks need amplification but this may be done at a later period, material might be available to carry this study to some distant time. Studies of factors of sex in infection and careful observations on given lots of the *Ornithodoros* rather than on exemplary individual ticks, are needed.

M. S. MARSHALL

EXPERIMENTAL INVESTIGATIONS OF MIXED INFECTIONS J. BURGEAS, Klin Wchnschr 9 1666, 1930

When injected into guinea-pigs streptococci did not increase the virulence of diphtheria bacilli. On the contrary, diphtheria bacilli increased the virulence of

the streptococcus. In mice the results were different, when nonlethal doses of diphtheria bacilli with half the lethal dose of a streptococcus culture were injected intraperitoneally, the animals died rapidly from a double infection. In other experiments it was demonstrated that diphtheria toxin does not increase the virulence of streptococci. Streptococci definitely increase the virulence of *B. influenzae* when injected together (subcutaneously or intraperitoneally). Likewise, on subcutaneous injection, influenza bacilli definitely increase the virulence of streptococci. Experiments with type I pneumococcus showed that the virulence is increased threefold by simultaneous injection of *B. influenzae*. The virulence of the influenza bacillus can also be increased fourfold by the simultaneous injection of pneumococci. The investigations were extended to include the saprophytes. It was shown that diphtheria or streptococcus toxin made *B. prodigiosus*, *B. vulgaris* and *B. subtilis* virulent, as did sublethal doses of streptococci.

CHARLES WEISS

THE BACTERIAL FLORA OF ULCUS CRURIS VARICOSUM. KARL BAERTHLEIN, Zentralbl. f. Bakteriologie **114** 1, 1929

This paper contains a detailed, tabulated analysis of the bacteriologic observations in varicose ulcer of the leg. The bacterial flora of the ulcer in 320 patients, was studied, smears and cultures being made in each case. For the latter, Loeffler's medium, ascitic agar and litmus lactose agar were used.

Of the 320 cases examined, staphylococci were present in 308, diphtheria and diphtheroid bacilli in 178, *Bacillus coli* in 98, streptococci in 66, *Bacillus proteus* in 25, *Bacillus pyocyaneus* in 22 and in a few cases, spirochetes, fusiform bacilli, yeasts, pneumococci, *Bacillus prodigiosus* and sarcinae were found.

The author considers that many of the diphtheria bacilli found were pathogenic, and in one patient he believes that symptoms of generalized toxemia resulted from their action. In this patient, an autogenous vaccine seemed to relieve the symptoms.

Baerthlein believes that the bacterial infection of varicose ulcer should not be regarded as that of harmless saprophytes but of definitely pathogenic micro-organisms. Consequently, antiseptic therapy and particularly autogenous vaccine therapy should be applied. For the vaccine, the mixed growth, suspended in saline solution and heated at 56 C. for one hour should be used.

PAUL R. CANNON

THE RETICULO-ENDOTHELIAL SYSTEM IN INFECTIOUS JAUNDICE. R. S. TSCHERIKOWER and P. L. RUBINSTEIN, Zentralbl. f. Bakteriologie **114** 65, 1929

The authors infected twenty-five splenectomized guinea-pigs and twenty-one controls with a weakly virulent strain of *Spirochaeta icterogenes* Verdun. Eight of the former and five of the latter died of infectious jaundice, therefore, no significant difference was evident as a result of the splenectomy.

PAUL R. CANNON

THE CURE OF WEIL'S DISEASE IN GUINEA-PIGS AFTER TREATMENT WITH BISMUTH-YATREN. A. P. UHLENHUTH and W. SLIFFERT, Zentralbl. f. Bakteriologie **114** 241, 1929

The authors confirmed their earlier results that Weil's disease in guinea-pigs may be prevented by treatment, within five days after percutaneous injection of the spirochetes, with bismuth-yatren. Furthermore, six weeks later the animals injected with the bismuth were found to be spirochete-free, as revealed by the injection of organ-emulsions into other guinea-pigs. Animals treated with a preparation containing a bismuth compound and chiniofon were immune to reinfection several weeks later and contained protective immune bodies in their serums. The authors believe, from an analysis of the data, that the therapeutic effect is not a direct spirocheticidal one but that the bismuth acts on the defense mechanism of the infected animals, thereby securing an increased response to the infecting micro-organisms.

PAUL R. CANNON

Immunology

SKIN REACTIONS TO *DIROFILARIA IMMITIS* IN PERSONS INFECTED WITH *WUCHERERIA BANCROFTI* WILLIAM H. TALIAFERRO and WILLIAM A. HOFFMAN, J Prev Med 4 261, 1930

A large proportion of persons infected with *Wuchereria bancrofti* exhibited an immediate positive skin reaction to the intradermal injection of about 0.025 cc of a 0.5 per cent saline extract of dried, powdered *Duofilaria immitis*. Control tests with other parasitic extracts gave negative results. The possession of pseudopods by the urticarial wheal was used as the criterion of positiveness. In this way, twenty-three persons known to be infected with the germ showed nineteen positive reactions, fifty-six persons possibly infected showed thirty-eight positive reactions, twenty-two persons probably uninfected showed one positive reaction, and nineteen persons known to be uninfected showed no positive reactions. In another series of experiments in which the criterion of positiveness was determined by the possession of pseudopods by the wheal, or a wheal 10 mm or larger in diameter with a concomitant negative reaction to some other parasitic extract, the twenty-three persons known to be infected showed twenty-one positive reactions, the fifty-six persons possibly infected showed forty-six positive reactions, the twenty-two persons probably uninfected showed one positive reaction, and the nineteen persons known to be uninfected showed no positive reactions. There seemed to be no correlation between age and reactivity either among infected persons or in the whole group of infected and noninfected persons. In five of eleven cases, sensitivity was passively transferred to a local area in the skin of non-sensitive persons by the injection of serum from a sensitive person ("local passive transfer"). In contrast to the immediate reaction, few persons infected with *Wuchereria bancrofti* exhibited delayed reactions to intradermal injections or extracts of *Duofilaria immitis*. Thus, of twenty-three persons known to be infected, only three exhibited marked delayed reactions, of thirty-nine persons possibly infected, two gave marked, four slight and three doubtful positive reactions, of twenty-two persons probably uninfected five gave very doubtful reactions, and of twenty-one persons known to be uninfected four showed very doubtful reactions.

AUTHORS' SUMMARY

THE UNION OF VACCINE VIRUS AND ITS SPECIFIC ANTI-SERUM IN VITRO
N. E. MCKINNON, J Prev Med 4 411, 1930

Experiments are presented that indicate that vaccine virus forms stable union in vitro with its specific antiserum, and that a certain duration of contact is required to effect the stability of the union. This is confirmatory evidence that the union of vaccine virus and its specific antibody is comparable to other antigen-antibody unions, without the intervention of alexin (complement). A question is raised in regard to the significance and interpretation of the dilution phenomenon. Perhaps the difference between these observations and those reported from other laboratories is due to the fact that dermal vaccine was used in the experiments here reported.

AUTHOR'S SUMMARY

IMMUNOLOGIC DIFFERENTIATION OF PALLIDA STRAINS F. PLAUT and H. KASSOWITZ, Klin Wchnschr 9 1396, 1930

Identical immune serums as tested by agglutination, spirocheticidal effect and complement fixation were obtained by the immunization of rabbits with cultures of two pallida strains and with pallida autolysates. These two strains differed immunologically from a third strain.

AUTHORS' SUMMARY

IMMUNOLOGIC CORRELATIONS BETWEEN HERPES SIMPLEX AND VACCINIA H. PETTE, Zentralbl f Bakteriol 114 185, 1929

Rabbits were given injections intracorneally with herpes virus, and the brain and cord were subsequently studied, both in normal rabbits and in others pre-

viously given injections intracutaneously or intracorneally into the other eye with vaccine virus. No immunity of any significant degree was found to result from previous treatment with vaccine virus. Also, the herpes encephalitis was uninfluenced in its histologic character by previous vaccination with vaccine virus.

PAUL R. CANNON

IMMUNITY IN EXPERIMENTAL SPOTTED FEVER. YOSHIAKI FUKUDA, *Zentralbl f Bakteriologie* **115** 83, 1929

Fukuda studied the effects in guinea-pigs of infection with the virus of spotted fever and observed an active immunity in each case in which the previous infection had been a normal, febrile one. The simultaneous injection of immune serum and virus caused a symptomless infection to develop, which, however, conferred an active immunity. He demonstrated that the virus develops in the symptomless infection, but that it is somewhat restrained by the immune serum.

PAUL R. CANNON

THE RELATIONSHIP BETWEEN INHIBITING SUBSTANCES FOR TUBERCLE BACILLI AND TUBERCULIN ALLERGY. M. SONAK, *Zentralbl f Bakteriologie* **115** 173, 1930

Sonak mixed 10 cc of blood and 25 cc of a freshly prepared suspension of human tubercle bacilli in a paraffined Wright capillary tube, sealed the tube in a nonparaffined capillary pipet and incubated it at 37 C. Shreds of the blood were then placed on sterile slides and incubated for nine days more, at the end of which time these were suitably prepared and stained to demonstrate the groups of tubercle bacilli that had grown. The results indicated a pronounced inhibition of growth in blood from children giving positive reactions to the tuberculin, while growth was favored in blood from children with measles taken during and shortly after the exanthem, as well as in two children giving negative reactions to the tuberculin.

PAUL R. CANNON

ORGANOSPECIFIC ELEMENTS IN BRAIN TISSUE. E. WIEBESKY and G. SALLAZZO, *Ztschr f Immunitätsforsch u exper Therap* **67** 1, 1930

Organospecific antibrain serum reacts in the brains of guinea-pig and human embryos. The reacting elements of the embryonal brain tissue are designated as "lipoids."

THE ACTION OF PHENOL ON THE ANTIGENIC PROPERTIES OF DIPHTHERIA TOXIN. L. TSCHERTKOW, *Ztschr f Immunitätsforsch u exper Therap* **67** 25, 1930

Phenol (0.5 per cent) weakens the antigenic powers of diphtheria toxin more rapidly than toluene.

BLOOD GROUPS IN ANIMALS. O. THOMSEN and T. KEMP, *Ztschr f Immunitätsforsch u exper Therap* **67** 251, 1930

The blood corpuscles of rabbits contain receptors that bind human anti-B agglutinin. In many rabbits the serum contains anti-A agglutinin for human corpuscles. Monkeys frequently have receptors for human anti-B agglutinin.

EXPERIMENTS WITH DIPHTHERIA ANATOXIN. M. P. ISABOLINSKY and V. I. GITOVITSCH, *Ztschr f Immunitätsforsch u exper Therap* **67** 441, 1930

Guinea-pigs were immunized by anatoxin not only against diphtheria toxin, but against diphtheria bacilli in pure cultures.

ANTIBODIES AGAINST LEUKOCYTES E WITFBSKY and K KOMIGA, Ztschr f Immunitatsforsch u exper Therap **67** 480, 1930

Leukocytes from guinea-pigs injected into rabbits led to the production not only of Forssman's heterogenetic antibodies, but antibodies against alcoholic extracts of guinea-pigs' leukocytes and spleen. In the rabbit species leukocytes from rats produced specific lipid antibodies, the action of which was not, however, limited to the leukocytes.

THE EFFECT OF A TUBERCULOUS FOCUS ON THE IMMUNE REACTIONS OF THE BODY L DIENES, Ztschr f Immunitatsforsch u exper Therap **68** 13, 1930

In experiments on rabbits it was found that the introduction of antigen into a local focus produced more marked results than intravenous injection into animals with similar foci. The removal by operation of the focus within a few hours after the injection of the antigen had no effect on the result. It is not possible to explain this result at the present time.

THE CHEMICAL NATURE OF THE HETEROGENETIC ANTIGEN IN SHIGA BACILLI KURT MEYER, Ztschr f Immunitatsforsch u exper Therap **68** 98, 1930

The carbohydrate fraction isolated from *Shiga* strains, which contain heterogenetic antigen units with the corresponding heterogenetic antibody. The heterogenetic antigen in *Shiga bacilli* is regarded as a carbohydrate.

ARRANGEMENT OF ENTEROCOCCI INTO TYPES KURT MEYER, Ztschr f Immunitatsforsch u exper Therap **68** 109, 1930

Ten strains of enterococci cultivated for more than ten years retained, with one exception, the original type of agglutination. Of sixty-eight new races, approximately 41 per cent could be arranged into four groups according to agglutination and complement fixation. As a rule, the results of agglutination and complement fixation agreed.

PURIFICATION OF HEMOLYSIN H VON EULER and E BRUNIUS, Ztschr f Immunitatsforsch u exper Therap **68** 124, 1930

By the absorption of a lysin against sheep blood with the stroma of sheep corpuscles and subsequent treatment with ammonia, a purified lysin of high titer was obtained.

Tumors

PRIMARY CARCINOMA OF THE FALLOPIAN TUBES R E WATKINS and W M WILSON, Surg Gynec Obst **51** 125, 1930

The lumen of the distal half of the right fallopian tube was replaced by a hemorrhagic, papillomatous, carcinomatous, oval tumor measuring 5 by 6 cm, which was surrounded by a tubal wall that contained lymphocytes, hypertrophied muscle fibers and tumor cells that had not invaded the serosa. The proximal portion of the tube had a patent lumen permitting a watery, blood-tinged fluid to escape into the vagina. The fimbriated end was occluded except for a small cyst containing a clear serous fluid. The frequent etiologic factors recorded in 200 authentic cases were lacking in this patient in that there were no evidences of long-standing pelvic inflammation. She had had ten full term pregnancies and no miscarriages; there were no wolffian remnants in the tube and subjacent structures, or any para-ovarian new-growths.

RICHARD A LIVENDAHL

CLASSIFICATION OF FOUR THOUSAND EXPERIMENTAL OIL AND TAR SKIN TUMORS C C TWORT and J M TWORT, *Lancet* 1 1331, 1930

The following tabulation briefly summarizes one portion of the classification

	Animals Used	Benign Tumors	Malignant Tumors
Coal gas tars	800	93	106
Synthetic tars	8,800	1,086	1,281
Shale oils	10,000	977	307
Petroleum oils	6,100	183	43
Other oils	500	0	0
Pure compounds	2,900	15	6
Totals	29,100	2,354	1,743

Mice were used in the work, and the types of tumors encountered were classed as arising from (a) the surface epithelium, (b) the follicular epithelium, (c) the sebaceous glands, (d) the connective tissue and (e) those composed of mast cells. The number of each of these tumors is not stated.

GEORGE RUKSTINAT

A CONGENITAL DIVERTICULAR RHABDOMYOMA OF THE BLADDER CHARLES HUETTE, *Ann d'anat path* 6 267, 1929

A detailed description is given of a rhabdomyoma in the bladder of a child 13 months old. The case reported is the sixth, only five have been previously described.

B M FRIED

A STUDY OF MELANOTIC TUMORS F ROULET, *Ann d'anat path* 6 489, 1929

Roulet affirms that melanotic tumors should not be classified according to their histogenesis. A cutaneous nevus, during its malignant transformation, is composed of two elements: nevus cells in a state of proliferation and the skin epithelium in a state of malignant segregation. The histologic picture of the tumor will depend on the preponderance of one or the other process. The nevus cell is a desmoplastic element which has lost its epithelial characteristics to acquire connective tissue functions. It is not its blastodermic origin which characterizes it but its virtual histofunctional differentiation. A pigmented nevus of the skin will develop into a tumor with sarcomatous as well as carcinomatous characteristics. According to histofunctional differentiation of the neoplastic cell, one will then speak of sarcomatous or carcinomatous melanoma or of melanosarcoma and melanocarcinoma, disregarding the blastodermic origin of the neoplastic element. The article contains a comprehensive review of the literature on this subject and reports of eight personal cases. A large bibliography is appended.

B M FRIED

EMBRYOMAS IN THE EVOLUTION OF CHORIOCARCINOMA LOUIS DE WALSCHÉ, *Arch internat de med exper* 5 557, 1930

A case of choriocarcinoma, occurring in a virgin, 16 years of age, is reported. A tumor, diagnosed after operative removal as embryoma, was found in the right posterior culdesac, partially embedded in the corresponding broad ligament. At autopsy, numerous metastases were found in the lungs, pleura, mediastinum, diaphragm, liver and mesentery. The uterus was normal. Microscopic examination of the metastases revealed tissue having the appearance of normal placenta, with syncytium and cells of Langhans. A comprehensive review of the literature is given.

J N PATTERSON

PAGET'S DISEASE OF THE NIPPLE AN EPIDERMOTROPIC CANCER C SIMARD, *Bull Assoc franç p l'étude du cancer* 19 50, 1930

The diagnosis of Paget's disease of the nipple is made when peculiar, large, clear cells are found at the level of the epidermis. The discussion is centered

around the origin of these cells. Some observers believe that they result from a dyskeratosis of the cutaneous layer, while others state that they have migrated to the skin from a preexisting mammary epithelioma. Simard is in favor of the latter opinion. He found morphologic similarities between the cells in Paget's disease and the cells in cases of migrated intramammary cancer. He observed cancers which had recently invaded the epidermis showing all the histologic traits of Paget's disease. And finally, in his experience, all of the clinical cases of Paget's disease of the nipple showed intramammary cancers. His arguments are supported by a detailed study of four cases of clinically diagnosed Paget's disease of the nipple and of six cases of intramammary cancer which had invaded the skin. Experiments with grafting cancer in the breasts of mice likewise supported his observations made on human subjects.

B. M. FRIED

CHRONIC CYSTIC MASTITIS C. A. HELLWIG, *Arch f klin Chir* **159** 763, 1930

Of 121 specimens from operations on the breast, 63 showed the changes typical of chronic cystic mastitis. Thirty-five were grouped as simple chronic mastitis, 2 as chronic cystic mastitis with marked epithelial proliferation and 3 as chronic cystic mastitis with atypical proliferation. Twenty specimens showed a combination of chronic cystic mastitis and carcinoma. The initial stages of chronic cystic mastitis are found in one third of all women over 40 years of age, according to autopsy determinations, on the other hand, half of the author's cases of cancer of the breast show cystic changes in the surrounding breast tissue. The opinion of those who regard chronic cystic mastitis as precancerous lesions and advise radical operation is rejected. The irregularity of the intraductal epithelial proliferation was so marked that a radical operation was advised. In only 3 of 40 cases, in which an infiltrating growth could not be found microscopically. Bleeding from the nipple is not a sign of malignancy, for it is observed also in benign lesions. The Wilson method of staining unfixed frozen sections with methylene-blue (methylthionine chloride, U. S. P.) proved reliable in the cases in which biopsy was performed during operation.

AUTHOR'S SUMMARY

THE GROWTH OF METASTATIC TUMORS OF THE BRAIN R. NISHII, Frankfurt *Ztschr f Path* **40** 1, 1930

This paper deals with the reaction of the tissue of the brain toward metastatic tumors. As a result of an investigation of six cases of metastatic carcinoma and five cases of metastatic sarcoma, the author concludes that the type of cellular reaction of the tissue of the brain is not essentially different in carcinoma and sarcoma. In the majority of cases, however, the metastatic carcinoma does not produce a marked reaction in the surrounding stroma, while the metastatic sarcoma is frequently surrounded by zones of softening or hemorrhage. The reaction of the brain is directed, first, against the infiltrating elements of the tumor, and second, against the mechanical compression of the tumor. The brain reacts toward the mechanical compression with the formation of glia fibers, connective tissue fibers, blood vessels and mast cells. Hemorrhages, necrosis and metabolic changes of the surrounding cells are caused by the invasion of the tumor. The question also is raised whether or not a metastatic sarcoma might cause a blastomatous transformation of the mesenchymal tissue.

CARCINOMA OF THE THYROID WITH EXTENSION INTO THE RIGHT AURICLE BY INVASION OF VEINS N. J. WYLEGSCHANIN, Frankfurt *Ztschr f Path* **40** 51, 1930

A woman, aged 50, had marked edema and cyanosis of the face. On section, a large portion of the thyroid was found to be replaced by a tumor that occupied almost the entire left lobe, the isthmus and a part of the right lobe. Both superior and inferior thyroid veins, both jugular veins and the subclavian and innominate

veins were filled with tumor thrombi that extended into the right atrium. The tumor consisted of epithelial cells arranged in masses and separated from one another by fibers of connective tissue. There was a slight tendency toward the formation of glandular structures throughout the tumor. In some portions the cells were arranged about blood vessels so as to resemble pictures seen in papilloma. Many tumor cells were encountered in the veins in the sections of the thyroid as well as in the sections of the larger veins and those of the atrial cavity.

HYPERNEPHROMA-LIKE TUMOR OF THE LEFT SUPRARENAL WITH METASTASIS
TO THE LIVER AND APLASIA OF THE RIGHT SUPRARENAL. A. SCHÜTER,
Frankfurt Ztschr f Path **40** 97, 1930

The case of a woman, aged 33, is described. The menses had stopped about five years before death. The blood pressure varied from 170 systolic and 110 diastolic to 210 systolic. At autopsy, an abundance of subcutaneous fatty tissue was present, in some portions measuring 5, in other portions 9 cm in thickness. In the axilla and around the pubic region, only a few hairs were found. There was a tumor, 5 by 8 by 11 cm in the region of the left suprarenal gland, apparently replacing it, with metastasis into the liver. Histologically, the tumor consisted of large vesicular cells, partly polygonal, highly stained and arranged into columns resembling those found in the fasciculate zone of the suprarenal cortex. No chromaffin or ganglion cells could be demonstrated. No evidence of medulla was seen within the tumor. The right suprarenal gland was absent. The ovaries showed marked fibrosis and atrophy, with complete disappearance of the follicles. The hypophysis offered an increase in eosinophilic cells with some decrease in basophilic cells. In explanation of the high blood pressure, the theoretical possibility is discussed of an overproduction of epinephrine by an overcompensation of the chromaffin system outside of the suprarenal glands, because of the aplasia of the right suprarenal and the absence of chromaffin cells within the tumor. The atrophy and fibrosis of the ovaries are taken as sequels to the tumor in the suprarenal gland, while the cessation of the menses and the generalized adiposity are believed to be signs of the incompetency of the ovaries.

CARCINOMA IN REGENERATING LIVER TISSUE. P. KOTIJARTSCHUK, Frankfurt
Ztschr f Path **40** 118, 1930

This article reports the case of obliterating endophlebitis of the hepatic veins which led to an atrophy of a large portion of the liver. These changes caused a regenerating hyperplasia in the tissue of the liver, which in some portions was the seat of a carcinoma. Histologically, the tumor showed small cells that varied in size. The nuclei were large, some lightly stained, others rich in chromatin. No tendency toward the formation of acini was noted. Some necrosis and hemorrhage were found throughout the tissue.

EFFECT OF RADIUM IRRADIATION ON CARCINOMA. J. WATJEN, Virchows Arch
f path Anat **275** 156, 1930

The effects of radium on the tissues of malignant tumors are difficult to determine because they are not readily distinguished from the changes that occur spontaneously in tumors. The examination of bits of human neoplasms removed by biopsy at intervals after irradiation is not satisfactory, because the biopsy procedure itself may cause regressive changes in the tissue, and because the small pieces that are thus removed do not permit the study of sufficiently large areas of tissue. The time of the appearance and the nature of the changes that may be ascribed to radium have been especially difficult to determine. Perthes was able to detect no change in tissue removed from a carcinoma of the breast on the seventh day after irradiation, although in another piece of tissue removed changes were evident on the seventeenth day. Watjen had the opportunity of studying microscopically the tissues of four patients who died in from one to six

days after the application of radium. All were elderly women, and in each the tumor was a carcinoma of the uterus. In each case, the radium was applied in the same institution, the dosage and filtration were approximately identical, and necropsy was done shortly after death. In one patient, hysterectomy for carcinoma of the body of the uterus had been done five years before death. Two months before death and again on the day before death, radium had been applied intravaginally for pelvic recurrence. Death resulted within twenty-four hours of the second application from pulmonary embolism. A second patient with squamous cell carcinoma of the cervix received two applications of radium within the cervical canal in the course of one and a half days. Two days after the second application stormy symptoms of pulmonary embolism developed when the radium capsule was removed. A pulmonary embolus was not found at necropsy. The third patient, also with squamous cell carcinoma of the cervix, received two intracervical applications of radium and died of pulmonary embolism three days after the beginning of the second application and six days after the beginning of the first application. In the fourth patient, a carcinoma of the body of the uterus was removed by curettage, and radium was inserted into the uterine cavity. Fever developed the next day, and death occurred on the fifth day. In the last case, no tumor tissue could be found within the uterus at necropsy, but the uterine tissue was freshly necrotic at the site of the application. An acute inflammatory reaction extended through the wall of the uterus and involved the covering serosa. In the other three cases, histologic changes are described in the tumor tissue that are held to be the immediate effects of radium. The earliest process noted was cessation of mitosis in the tumor cells. The nuclei revealed evidences of degeneration, and the tumor cells became necrotic. The regressive changes were most marked immediately beneath the site of application of the radium. These alterations Watjen believes can be differentiated from the spontaneous regressive changes occurring in other parts of the tumor. The vessels of the tumor stroma about the areas of parenchymal necrosis due to radium were engorged and contained an increased number of leukocytes, and the stroma itself was sometimes infiltrated by leukocytes. The stroma reaction, the author believes, is secondary to the changes caused by the radium in the tumor parenchyma, and not due to the action of the radium directly on the stroma itself. Watjen points out that the application of radium in elderly persons is not without danger. When applied within the uterus, and especially after curettage, he believes that it may lead to bacterial invasion of the tissue with resulting thrombosis, and to death from infection or pulmonary embolism.

O T SCHULTZ

THE RESPONSE OF BLOOD VESSELS TO EXTRACTS OF TUMORS. M. LAPIDARI, *Ztschr f Immunitätsforsch u exper Therap* **67** 159, 1930

The isolated vessels of tumorous chickens, rats and mice respond more actively to the extracts of the homologous tumor than do the vessels of normal animals.

COMPLEMENT-CONTAINING ANTIBODIES IN PATIENTS WITH CANCER AND IN PREGNANT WOMEN. L. HIRSZFELD and W. HAIER, *Ztschr f Immunitätsforsch u exper Therap* **67** 286, 1930

In a large percentage of patients with cancer complement-binding antibodies were found that reacted with alcohol soluble extracts of cancer tissue. In 60 per cent of pregnant women, the serum was found to react with the cancer extracts.

THE DEMONSTRATION OF SPECIFIC ANTIGENS IN CANCER TISSUE. H. LEHMANN-FACIUS and T. TODA, *Ztschr f Immunitätsforsch u exper Therap* **67** 373, 1930

When suspensions of carcinomatous tissue, boiled for half an hour at 100 C., were injected into rabbits, the serum acquired the power of elective fixing complement in carcinoma cells.

Medicolegal Pathology

DISTRIBUTION OF ARSENIC IN THE BODY S BLUMENFELDT, Deutsche Ztschr f d ges gerichtl Med **15** 501, 1930

A study to establish the amount of arsenic in various organs, ingested at various times was undertaken. By comparing the quantities of arsenic in the gastro-intestinal canal with those obtained from the analysis of the liver, one cannot draw a definite conclusion as to whether a certain amount of arsenic was administered in one or more doses. In cases in which arsenic poisoning is suspected, one should examine chemically not only the internal organs but the hair, since arsenic will be found in the hair even when the stomach does not show any traces. Instances in which arsenic is found in relatively large quantities in the gastric contents while it is completely absent in the hair, prove to be cases of acute arsenic poisoning. Should the hair contain more arsenic than the stomach, one can conclude that one or more doses of the poison were ingested at some time prior to death. Presence of arsenic in the hair and in comparatively large amounts in the stomach proves conclusively that arsenic was given at different times. Only from the comparison of detected quantities of arsenic in the hair and in the gastric contents is one able to conclude whether the poison was administered once or several times.

E L MILOSLAVICH

AN UNUSUAL OBSERVATION IN AN EXHUMED, PUTREFIED BODY B PUCHOWSKI, Deutsche Ztschr f d ges gerichtl Med **15** 532, 1930

At the autopsy of a man, aged 20, whose body was disinterred two months after death because poisoning was suspected, numerous small, round, yellowish-white nodules, the size of a pinhead, were scattered on the cut surfaces of the lungs. Similar nodules were found on the endocardium and valves as well as between the chordae tendineae. The chemical and microscopic examinations disclosed that these tiny bodies were chiefly of mineral character (calcium phosphate, calcium carbonate) and contained also traces of fat, endothelial cells, and cocci and rod-shaped bacilli. Similar formations may occur on the mucous surface of the intestines. These nodular, mineral deposits are the result of putrefaction.

E L MILOSLAVICH

BLOOD GROUPS IN PATERNITY CASES KNUDT SAND, W MUNCK and J G KNUDTZON, Deutsche Ztschr f d ges gerichtl Med **15** 535, 1930

This is a report of the first 500 cases of questions of paternity in which determinations of blood groups were made at the medicolegal institute of the University of Copenhagen.

SUICIDE BY STRANGULATION P FRAENCKEL, Deutsche Ztschr f d ges gerichtl Med **15** 564, 1930

The author describes in detail two cases in which self-strangulation was committed in an unusual manner. In the second case, cataleptic rigor mortis occurred and illustrated the mechanism of the strangulation, viz, the position of the hand holding the loose ends of the cord.

E L MILOSLAVICH

Technical

THE NATURE OF THE GRAM COMPOUND ALLEN E STEARN and ESTHER WAGNER STEARN, J Bact **20** 287, 1930

The cell wall theory of the Gram reaction in its ordinary form necessitates the existence in the decolorizer solution of large dye-mordant molecules. Absorption spectrums indicate the presence of only free dye and free iodine in

solutions of methyl violet-iodine precipitate in both alcohol and acetone. The boiling point elevation of a solution of methyl violet-iodine precipitate in acetone indicates complete dissociation into iodine and dye. These observations indicate a high degree of improbability for the ordinary cell wall mechanism for the Gram reaction, but they are in no way contradictory to the chemical mechanism formerly proposed by the authors. Results also indicate that through chemical treatment and starvation the bacteria gradually lose gram-positivity and show a stippled appearance of gram-positive granules.

AUTHOR'S SUMMARY

DRIED SERUM FOR DETERMINING BLOOD GROUPS. M. CISER and N. KOVACS, *Munchen med Wchnschr* **77** 709, 1930

Favorable results with dried serum are reported and an improved method of preparing it is described. Properly dried serum may be stored for a long time without loss of potency.

INJECTION METHODS IN EXPERIMENTAL SYPHILIS OF RABBITS. WERNER WORMS, *Zentralbl f Bakteriol* **114** 355, 1929

This is an illustrated article discussing operative methods and anatomic relationships for the more accurate study of syphilis in rabbits. References to German textbooks on the anatomy of experimental animals are given.

PAUL R. CANNON

A METHOD FOR THE DETERMINATION OF THE TOTAL NUMBER OF BACILLI IN SPUTUM. E. BUTSCHOWITZ, *Ztschr f Tuberk* **55** 321, 1930

A measured amount of sputum is digested with sodium hydroxide and neutralized. A suspension of yeast cells is added and well mixed. A smear of this mixture is stained for tubercle bacilli, and the relative number of tubercle bacilli and yeast cells is determined. The number of yeast cells in the original suspension is determined by counting in a hematologic counting chamber. These data permit a simple calculation from which to estimate the actual number of tubercle bacilli in the sputum.

MAX PINNER

Society Transactions

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, Dec 8, 1930

JOSEPH A. CAPPS, *President, in the Chair*

OSTIUM FIBROSA IN THE SKULLTON OF A PREHISTORIC AMERICAN INDIAN HENRI S. DENNINGER

The complete report will be published in the ARCHIVES OF PATHOLOGY

DISCUSSION

E. R. LONG The number of studies of diseases of prehistoric inhabitants of this country is limited, and there seems to be considerable opportunity for further research. There is the possibility of gaining information by the study of any calcified masses of tissues and concretions that may be found associated with such skeletons.

PROTECTIVE AND COMPLEMENT-BINDING SUBSTANCES IN THE SERUMS OF PERSONS CONVALESCENT FROM YELLOW FEVER N. PAUL HUDSON

Immune substances have been demonstrated in the serums of five persons convalescent from laboratory infections with yellow fever. The serums of four were examined periodically during illness and convalescence, and that of the fifth several months after recovery. Unavoidable circumstances prevented the examination of all at regular intervals.

Protective substances were demonstrated by the survival of monkeys given injections of the serum and then injections of yellow fever virus (monkey blood). The serum of one patient, taken on the third and fourth days after the onset of illness, did not protect, but that taken on the fifth and eighth days did protect, the serum of another patient, taken on the third day, had no effect, but that taken on the sixth and eighth days protected, the serum of the third patient, taken on the second and fourth days, did not protect, but that taken on the seventh day did, the serum of the fourth patient gave no protection on the third day, but had protective properties on the fifth and seventh days, and the serum of the fifth patient, tested several months after recovery, repeatedly demonstrated protective properties. It seems, then, that substances protective against the yellow fever virus appear about the fifth day after the onset of illness.

Frobisher (*Proc Soc Exper Biol & Med* **26** 846, 1929, and other articles in press), Davis (in personal communications to the author and in reports to the International Health Division of the Rockefeller Foundation) and Aragão (*Compt Rend Soc de biol* **99** 1341, 1928) have reported experiments with complement fixation. The first two workers were successful, the last not. The following technique was found to give the best results. The antigen is serum from infected monkeys, pooled and dried while frozen, and stored in sealed containers in weighed amounts. It is effective for at least thirteen months. Normal monkey

serum similarly stored has no complement-fixing property. The other reagents are two units of guinea-pig complement, the test serum, two units of rabbit amboceptor, and a 2 per cent suspension of sheep's red blood cells. The total volume is 3 cc. Primary incubation is in the refrigerator at 5 C for about sixteen hours (over night), and the secondary incubation is in the water bath at 37 C for one-half hour. In carrying out the test, the antigen is diluted over a range of from 1:20 to 1:1,000, the serum concentration is constant, in a dilution of 1:5. Positive tests frequently manifest a prozone. The usual controls are made.

The results of complement-fixation tests during and after convalescence of the persons here considered were as follows. The serum of one convalescent person gave the first positive reaction in the ninth week after the onset of illness, and continued to give positive reactions for nine months after the attack, the serum of the second convalescent person fixed complement in the eighth week and not before, the serum of the third gave a definite, but not strong, reaction in the thirteenth week, in the only examination made thus far, that of the fourth repeatedly failed to fix complement seven months after the onset of the illness, and the serum of the fifth, tested for the first time eight months after the attack, showed complement fixation and continued to do so twenty months after the illness.

Thus, the serums of four persons convalescent from yellow fever had complement-fixing properties beginning a number of weeks after the acute illness, and the serum of one failed to have these after seven months.

DISCUSSION

PAUL CANNON. Does the serum protect if given after the infecting dose, and if so, within what length of time must it be given?

H. P. HUDSON. If the protective serum and the infecting dose are given simultaneously, the animal lives, but if the serum is given as much as twenty-four hours after the infecting dose, there is no protection in monkeys. Protective serum given before the infecting dose is effective for six weeks.

MELANOCARCINOMA OF THE GALLBLADDER S. R. ROSENTHAL

A colored man, aged 48, entered Cook County Hospital completely disoriented. According to his wife, he had been in this condition for two days. The only additional information was that he had had lumbar pain and hematuria for two months. The physical examination revealed a bilateral papilledema with hemorrhages, a right lower facial paralysis and absence of abdominal and left cremasteric reflexes. The coordination was poor, and the patient fell to the left side. The spinal fluid was bloody and under increased pressure, and the result of the Wassermann test was strongly positive. The urine was unchanged. The patient died thirteen days after the onset of the cerebral symptoms.

Postmortem examination revealed a pedunculated primary melanocarcinoma of the gallbladder with metastases to the brain, lungs, jejunum and left kidney. All other possible primary sites of melanotic tumors were excluded, such as the skin, the meninges, the brain, the eyes and the rectum.

This report emphasizes that melanotic tumors are epithelial in origin, and that the melanin is formed in the cytoplasm of these cells, as a uniform, finely or coarsely granular pigment varying in color from light to dark brown. In contrast with this conclusion, the cytoplasm of the chromatophores of Ribbert contained an irregular, coarsely granular pigment ranging from dark brown to black.

The complete report will be published in the *American Journal of Cancer*.

RUPTURED ANEURYSM OF THE CYSTIC ARTERY OF THE GALLBLADDER AS A RESULT OF TOXIC ARTERITIS S. R. ROSENTHAL

The complete report will be published in the *Archives of Pathology*.

PATHOLOGIC DISSIMILARITY IN TWO CLINICALLY SIMILAR CASES OF BLOOD DYSCRASIA L BLEYER and CHARLES ULRICH

The complete clinical records and the results of examinations of the blood of two patients are reported, with a brief review of the literature. One patient had acute lymphatic leukemia, which terminated fatally within a week, and another had so-called "infectious mononucleosis," which progressed slowly to complete clinical recovery after eight months. The blood, however, still shows slight abnormalities.

The similarities and dissimilarities in the blood of these patients were discussed. Infectious mononucleosis may represent a functional lability of the lymphatic system with a possible predisposition to lymphatic leukemia in later life. Examinations of the blood of patients with this condition should be made over a sufficient length of time to determine the ultimate outcome.

The complete report appeared in *J A M A* **96** 191 (Jan 17) 1931

DISCUSSION

JOSEPH A CAPPS. Patients with "mononucleosis" have great clinical interest. I have thought that these cells probably came from the reticulo-endothelial system rather than from the lymphoid tissues. They are seen in the blood with a great many diseases.

R H JAFFL. Supravital stains are necessary to determine more accurately the nature of these cells.

MUCOCELE OF THE APPENDIX, WITH A DIVERTICULUM AND INVAGINATION INTO THE CECUM F W MULSON

Mucocele of the appendix is rare and is seldom recognized clinically. It is found most often during postmortem examinations or during operations for chronic abdominal conditions, and in the male is the most frequent cause of pseudomyxoma peritonei. Phemister (*J A M A* **84** 1834, 1925) stated that an acute inflammation requiring immediate surgical relief rarely develops. Other complications are intussusception, invagination, volvulus, intestinal obstruction and hernia. Dodge (*Ann Surg* **63** 335, 1916) found 142 reports, of which 55 were based on tissues obtained postmortem, 66 on tissues obtained by operations, and 21 on cases without these details. Chronic inflammation was reported in 45, diverticuli in 12 and pseudomyxoma peritonei in 14. Weaver (*California & West Med* **29** 500, 1928) stated that 168 reports had been recorded. Since then Topping (*California & West Med* **29** 186, 1928) and Vorhaus (*J A M A* **94** 165, 1930) have added two more.

This condition is due usually to constriction or obliteration of the lumen in the proximal portion of the appendix by scar tissue, a neoplasm or a kink at the base. In most instances the lumen is obliterated, and the retained material is a sterile, viscid secretion. In the case reported by Vorhaus, barium was demonstrated in the lumen by the x-ray film. Castle (*Ann Surg* **61** 582, 1916) thought that the lesion in his patient may have resulted from the scarring of typhoid ulcers. Phemister attempted to reproduce the condition in dogs by closing the lumen, but acute appendicitis developed or the lumen was reestablished. A discussion and review of the size, shape, chemical contents, occurrence, etiology, morbid anatomy, diagnosis, etc., has been made by Morrison (*Boston M & S J* **188** 533, 1923) so that further discussion of these points seems unnecessary. I have not found in the literature a report similar to the account here given, in which invagination of the appendix into the cecum with resulting gangrene of the cecum is described.

A man, 47 years of age, without previous gastro-intestinal disturbances, except typhoid fever at the age of 14 years, had, in 1926, a right inguinal hernia, which healed in about one year with the use of a truss. During the months of April and May 1928 he had several attacks of pain and distress in the lower right

quadrant of the abdomen, which seemed to be relieved by rest or by the use of laxatives. During the following summer he had no further symptoms, and his bowels moved regularly without laxatives. About the middle of November, 1928, the pain and abdominal distress returned. He noticed in the lower right quadrant of the abdomen, a hard, tender mass, which did not disappear with the use of laxatives. He consulted his physician on Dec 5, 1928, who noticed the tender mass in the region of the appendix. There was no nausea or fever. After three days without relief the patient entered the hospital. The surgeon found the abdomen flat, that there was no rigidity of the muscles, and that a palpable tender mass was present in the region of the appendix. The temperature was 102 F, and the blood contained 17 000 leukocytes per cubic millimeter. The clinical diagnosis was acute appendicitis with a possible abscess.

The surgeon found that the spherical enlargement of the proximal end of the appendix had invaginated into the cecum. The pressure had impaired the blood supply to the cecum and had caused gangrene, especially of that portion covering the proximal end of the enlarged appendix. The appendix and the gangrenous portion of the cecum were removed, and the patient made an uneventful recovery.

The appendix was 9.5 cm long. The spherical proximal portion was 4 cm in diameter, and the remaining part was 5.5 cm long and 2.2 cm in diameter. Near the distal end along the mesentery, was a large diverticulum, which was 2 cm in diameter at the base and which projected 1.3 cm. The blood vessels of the serosa of the appendix were distended with blood. The mucosa of the cecum covering the tissues invaginated into the cecum was discolored and gangrenous. The wall of the diverticulum was less than 1 mm thick. The wall of the appendix was 5 mm thick, and that of the spherical part was from 3 to 4 mm thick. The lumen was filled with a clear, gelatinous material, in which were a few gray threads. There was no lumen in the proximal end. The wall of the diverticulum consisted of a thin layer of connective tissue, covered with a serous surface. There were extensive scarring of the wall of the appendix and hypertrophy of the smooth muscle tissues. Only small portions of the mucosa had lining epithelial cells. Secreting epithelial cells were not found. There was acute inflammation and necrosis of the wall of the cecum covering the invaginated part of the appendix.

Mucocele of the appendix is rarely an acute surgical condition. The presence of a diverticulum of a mucocele is even more rare and is very suggestive of the method of development from an appendix of the condition known as pseudomyoma peritonei. The invagination of such an appendix into the cecum with resulting gangrene of the cecum is a rare condition. At least no similar report was found in the available literature.

Book Reviews

A TEXT-BOOK OF HISTOLOGY By ALEXANDER A MAXIMOW, Late Professor of Anatomy, University of Chicago Completed and Edited by William Bloom, Assistant Professor of Anatomy, University of Chicago Cloth Price, \$9 Pp 833, with 604 illustrations, some in colors Philadelphia W B Saunders Company, 1930

From the preface we learn that at the time of his death in December, 1928, Professor Maximow was writing a textbook of histology. Much material and many illustrations had been collected. The sections on the generative organs, the urinary tract, the organs of special sense and epithelium had been completed. The sections on the blood and connective tissue, the gastro-intestinal tract, the vascular and lymphatic systems, the spleen, the skin and the mammary gland were left in rough manuscript. The book has been completed and edited by William Bloom, who has written the sections on the biliary and respiratory systems, the pancreas, the endocrine glands with the exception of the suprarenals (which are described by N Hoerr) and the introductory chapter. With the help of Prof C Judson Herrick he has also compiled, from various sources, including a Russian text by Professor Maximow, the chapters on the nervous tissues. Professor Bloom deserves a great deal of credit and praise for his faithful and arduous work without which the book could not have been completed. The result is a magnificent textbook of histology, superbly illustrated, which in general reflects faithfully the ideas of its masterful originator. The book is based so far as possible, with respect to both text and illustrations, on human material. It covers the field of histology completely, except that it does not include placentation and general embryology or the detailed structure of the brain and the spinal cord. However, it does include a description of the histogenesis of tissues and organs whenever it aids in understanding the mature structure. Technical matters and, in large measure, bibliographic references have been omitted in order to avoid much unnecessary duplication of matter already in print. The functional aspects of the structures described are not neglected, but receive interesting consideration under the heading "Histophysiologic Remarks." The style is clear and vigorous. As is well known, Professor Maximow was an active champion of the so-called unitarian theory of the formation of blood and connective tissue, and the results he obtained in his splendid work on vital staining and on the cultivation of tissue were interpreted in the light of this theory. The cells and tissues in question, their interrelationships and potentialities and other problems are considered in detail in chapters 3, 4 and 5, which deal with blood and connective tissue, and with blood-forming and blood-destroying tissue. Many pathologists will be greatly interested in these chapters, and the book will be an invaluable help to the student of pathologic histology and histogenesis.

LEGAL MEDICINE AND TOXICOLOGY By RALPH W WEBSTER, M D, PH D, Late Clinical Professor of Medicine (Medical Jurisprudence) in Rush Medical College, University of Chicago, Chicago Cloth Price, \$8.50 Pp 862, with illustrations Philadelphia W B Saunders Company, 1930

The object of this book, by the late Dr Ralph W Webster, is "to present in one volume the more usual phases of Legal Medicine in a somewhat concise manner, in order that the busy practitioner may have access to the more important points involved in the cases with which he, ordinarily, comes in contact and upon which he may be called upon to inform himself before giving testimony in such cases, and also in order that the student may have a presentation before

him, so that he may be able to learn the rudiments of the science and may prepare himself for the different examinations for licensure."

After an introductory chapter dealing with definitions, ordinary and expert witnesses and legal procedure, the volume is divided into two parts. Part I, Legal Medicine, occupies slightly less than 300 pages and deals with such subjects as legal rights and obligations of physicians, malpractice, identification of the living and the dead, postmortem observations characteristic of death from various causes, wounds and their medicolegal aspects, examination of blood stains, etc. These subjects are considered briefly, but perhaps adequately for the purposes of the book. Part II, Toxicology, consists of more than 500 pages. In his preface the author states that the apparent undue stress laid on toxicology in this work is due to the fact that he "has thought it advisable to go much more thoroughly into the methods of isolation and identification of the various poisons discussed than is the case with other single-volume works on the subject." Numerous cases of poisoning, sometimes on a wholesale scale, are cited. The commoner poisons are discussed in considerable detail, for example, about 65 pages are occupied by the discussion of arsenic.

The illustrations are not numerous and are not especially distinctive. References to the literature are reasonably abundant. The typography is satisfactory. A well arranged table of contents of ten pages is inserted at the beginning, and a full index of thirty-one pages at the end of the book.

This volume does what the author stated was his object, as quoted at the beginning of this review. It can therefore be recommended to those in need of a reliable and fairly brief textbook on the subject of legal medicine and toxicology.

DER APPENDICITISCHE ANHANG SEINE ETIOLOGIE UND PATHOGENESE. BY LUDWIG ASCHOFF. Mit Einem Kurzen Beitrag über die Lymphgefäßverhältnisse am Menschlichen Wurmfortsatz von Dr. H. Seng. Price, 12 40 marks. Pp. 125, with 36 illustrations. Berlin: Julius Springer, 1930.

This is the first in a new series of monographs on clinicophysiological problems considered particularly from the anatomic and pathologico-anatomic point of view. The problems may lie in any part of normal and pathologic anatomy on the one hand and in the clinical or pathologic physiology on the other hand, but they are to illustrate the relationship between the morphologic and the physiologic lines of thought, and in each case the problem will be discussed by an active investigator in the field in question on the basis principally of his own work. Aschoff discusses acute appendicitis, its cause and genesis, in five chapters, the titles of which will indicate the scope of his discussion: anatomic and physiologic preliminaries, including the lymph vessels of the appendix, by H. Seng; investigations of the etiology of appendicitis, the pathogenesis of acute appendicitis, conclusions and clinical hints. The investigations of the etiology includes bacterioscopic studies of smears and of sections of acutely inflamed appendices as well as cultures. The bacterioscopic studies are regarded as highly significant, because they establish the forms of the bacteria that were subjected to phagocytosis and that consequently may be assumed to be active infectious agents. An important outcome of the bacteriologic work is the demonstration that the bacterial flora of the distal third of the appendix is peculiar and contains the bacteria that are found in the acutely inflamed appendix. The most common bacterial agent in acute appendicitis appears to be the so-called enterococcus or intestinal streptococcus, then come the pneumococcus, the colon bacillus, a small gram-positive rod and an influenza-like rod. It is believed that retention in the distal end increases the virulence of appendiceal flora and thus favors the acute attack, which is enterogenic and begins on the surface of the mucous membrane. The presentation is clear and simple. The illustrations are excellent. The monograph is an important addition to the literature on acute appendicitis and sets a high standard for the subsequent numbers of the series. Practical pathologists will be interested especially in the instructive survey of the results of the examination of 1,000 appendices and in the thoughtful review of errors in clinical diagnosis.

MOLDS, YEASTS, AND ACTINOMYCETES A HANDBOOK FOR STUDENTS OF BACTERIOLOGY By ARTHUR T. HENRICI, M.D., Professor of Bacteriology, University of Minnesota Cloth Price, \$3.50 net Pp 296, with 100 illustrations New York John Wiley & Sons, Inc., 1930

This book is the outgrowth of a lecture course that has been offered at the University of Minnesota for some years. It was designed to fill the gap between the brief and inadequate discussions of the fungi found in many textbooks of bacteriology, and the extensive monographs and technical articles which have been written on the particular groups. Henrici has gone far in accomplishing his aim. The discussions of the several groups are necessarily brief, but he has succeeded in presenting much of the newer knowledge. The book will serve a useful purpose as a source of information in a field where few tread with much assurance. It should be of interest to microbiologists working in the various fields of applied microbiology, and especially to medical bacteriologists who have not always shown much familiarity with the uncommon fungi as causes of infections. If Henrici's book will help to drive from usage the terms "blastomyces" and "blastomycosis" alone, its appearance will have been vindicated.

The material is organized in eleven chapters as follows: I The Structure and Classification of the Fungi, II Methods for Studying Molds, Yeasts, and Actinomycetes, III Biological Activities of the Molds, IV Molds Belonging to the Phycomycetes, V Molds Belonging to the Ascomycetes and Fungi Imperfecti, VI The Dermatomycoses, VII Fungi Transitional Between Molds and Yeasts, VIII Oidium and Monilia, VIII Morphology and Classification of the Yeasts, IX Biological Activities of the Yeasts, X Morphology and Classification of the Actinomycetes, XI Biological Activities of the Actinomycetes.

Little more need be said about the contents, since the headings of the chapters suffice. The book is to be recommended to students of mycology, who need a general discussion of yeasts, molds and actinomycetes.

SELECTED READINGS IN THE HISTORY OF PHYSIOLOGY Edited by JOHN FAHRQUHAR FULTON, M.D., Formerly Fellow of Magdalen College, Oxford, Sterling Professor of Physiology, Yale University Price, \$5 Pp 317, with 60 illustrations Springfield, Ill Charles C Thomas, 1930

This book is patterned after Long's "Readings in Pathology" by the same publisher. It reproduces original passages that have exercised a marked influence on the development of physiologic knowledge. In order to secure a desirable sequence in various fields, the readings have been grouped chronologically according to subject as follows: general principles, circulation of the blood, the capillaries, respiration, digestion, muscle and peripheral nerves, the central nervous system and miscellaneous. Each section is preceded by a brief introductory explanation by the editor, who also writes brief but valuable biographic notes of the authors whose works are cited. The passages are taken from the earliest editions of the works in question. Full bibliographic description is given of each publication cited. In all English passages the original spelling and punctuation have been preserved, selections from other languages are given either in contemporary or fresh translations. The sixty illustrations are well chosen and refreshingly unconventional. The publisher's task is well done. From the editor's preface one learns that "of the 65 selections of which information was available concerning the age of the author when the work was done, 11 were written between 20 and 30 years of age—Mayow and de Graaf being 23, Arrhenius 24, and Helmholtz (Conservation of Energy), Blagden, Cannon and Herbert Mayo 26, 23 were written between the ages of 30 and 40 years, and the remaining 42 were written when their authors were over 40." The frequency with which important conclusions have been based on the results of experiments on human beings is also illustrated by the selections. Fulton's "Readings" is a valuable book. To the interested student it will be a stimulus, because it provides direct contact with the original source of great physiologic discoveries and contributions.

A SYSTEM OF BACTERIOLOGY IN RELATION TO MEDICINE Medical Research Council Volume 7 Virus Diseases, Bacteriophage Cloth Price, per volume, 1 pound, 1 shilling, net Pp 509 London His Majesty's Stationery Office, 1930 (May be obtained from the British Library of Information, 551 Fifth Avenue, New York)

The first five volumes of the Medical Research Council's system of bacteriology have been received with marked favor. Its standing as a contribution of great value to the literature of bacteriology in relation to medicine may be said to be assured. Volume 7 measures up to the standards of its predecessors. It deals with virus diseases and bacteriophage. Virus diseases of plants, animals and man are discussed in 38 chapters (450 pages) by about 27 British workers in microbiology. Within comparatively small compass are presented valuable critical summaries of the present knowledge of viruses and virus diseases, their nature and causes. About 18 human diseases currently accepted as of the virus class are considered. Apparently the recent outbreaks of parrot fever occurred after the printing of the volume was under way as this fever is not discussed. The statement at the bottom of page 185, about the epidemiology of infantile paralysis in the United States, is highly erroneous and should be corrected so far as possible. The only illustrations in the volume are of cell inclusions in certain virus diseases — "virus bodies" — and changes in the central nervous system in encephalitis and epidemic poliomyelitis. Each chapter is provided with an adequate list of references.

In the last chapter of the volume F. M. Burnet of Melbourne gives a good account of bacteriophage and cognate phenomena.

Books Received

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THE BLOOD PROTEINS

WITH SPECIAL REFERENCE TO THE CHANGES OCCURRING
IN RENAL DISEASES¹

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The purpose in this work has been to make a study of the changes in the proteins of serum and plasma especially in renal diseases, but also in some other conditions

TECHNIC

In the earlier analyses, the proteins were determined with the refractometer, and according to the technic of Robertson. But since it was suspected that the values as determined by this method were too high in the case of lipemic, milky serums, other methods were employed. The nonprotein nitrogen was determined by the method of Folin and Wu, the fibrinogen and total globulins were precipitated according to the method of Howe, and total and albumin nitrogen determined by the micro-Kjeldahl technic of Beiglund.

THE PROTEINS OF NORMAL SERUM AND PLASMA

Observations Recorded in the Literature—In a normal person the protein content of the serum is subject to considerable variation. A slight increase has been observed after a cold bath (von Farkas) and after muscular exercise (Reisz, Bohme). Pressure, congestion (Bohme) and stasis resulting from the application of a tourniquet cause a marked rise in the protein concentration. Reisz found that in venous congestion the refractive index of the serum increased from 59.03 to 74.69, while in stasis (tourniquet) there might be an increase in serum protein of as much as 0.4 Gm. per hundred cubic centimeters. The same has been found after the removal of large amounts of pleural or peritoneal fluid (Barlocci). An increased carbon dioxide content of blood likewise produces a transient rise in the serum proteins, which however, at once returns to normal if the acidity is increased (Bohme).

There is a fairly constant drop in the serum protein concentration following severe hemorrhage and menstruation (Reisz, Oliva).

Changes in body temperature and perspiration have an inconstant effect. According to Sandelowsky and Bohme, the blood becomes more

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* From the Department of Pathology of the University of Minnesota.

concentrated Reisz at times found just the opposite. A seasonal variation is also possible (Reisz).

Drinking pure water produces no appreciable change in the serum concentration of normal individuals (Engel, Schall). The administration of large quantities of sodium chloride caused a transient thickening of the serum even in the presence of a slight disturbance of the normal water balance (Benzel). Reisz, on the contrary, found a transitory thinning.

In a normal person, an average diet produces no constant or appreciable change in the concentration of the serum protein (Reisz, Tiantel and Rowe, Kahn, Bohme). The effect of starvation is open to question. Reisz stated that there is an increased concentration of the serum proteins, due to dehydration. Geill, in a review of the literature to 1927, was unable to find either an increase or a decrease reported.

The differences in serum proteins as between males and females are, at most, small and insignificant. Tiantel and Rowe found a slightly higher globulin in females, while Lewinski was able to find this only in pregnancy. Geill and Salvesen concluded that the differences are negligible. The total serum protein is low in new-born infants, but increases rapidly with age, so that adult values are reached at the age of about $1\frac{1}{2}$ years or soon thereafter (Reisz, Stahlberg, J. Munk, Geill).

It has been found, however, that, if the variations mentioned are guarded against, the concentration of the serum protein of a given individual is remarkably constant from day to day (Bohme, Muschel).

Much depends on the technic used, and values for the serum proteins must be interpreted accordingly, both in the normal and in the pathologic case. The older analysis, for the most part, consisted in precipitating the total serum protein with some salt, such as ammonium or magnesium sulphate, drying and weighing. Frequently the precipitated protein was unpurified, yet this is an important step. Reisz pointed out that the values for total protein found by this direct method were considerably higher than those secured by the Kjeldahl method, unless the precipitates were purified. The results were then much more uniform. Linbeck and Pick, in making a similar comparison, found that the results varied all the way from 0.8 to 21.5 Gm per hundred cubic centimeters.

The serum protein values determined by the refractometric method have been found to be a little higher than those calculated from the Kjeldahl method (Reisz, Linder, Lundsgaard and Van Slyke). The refractometer readings are, no doubt, much too high in the case of lipemic serums (Epstein). Rowe, using Robertson's technic, found a fair agreement between his results and those secured by the Kjeldahl method. He pointed out that as previously shown by Schorer, since there are marked variations in the albumin-globulin ratio in various

diseases, and since these fractions have different refractive indexes, the figures for total serum protein calculated according to the method and tables of Reisz are frequently erroneous. Reisz stated that the difference between his method and the direct method was only about

TABLE 1—*The Proteins of Normal Serum and Plasma (from the Literature)*

Investigator	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent	Fibrin, per Cent
Berzelius,* 1831	8.0			
Marett, 1831	8.7			
Denis,* 1838	8.0			
Iecanu,* 1837	7.8 to 8.1			
Bostok,* 1842	10.0			
Nasse, 1836	7.2 to 9			
Becquerel and Rodici,* 1845	8			
Otto, 1848	7.5 to 8			
C. Schmidt,* 1850	7.4 to 8.3			
Leven,* 1873	7.9			
Hammarsten, 1878	7 to 8.1	3.85 to 5.3	2.48 to 3.74	
Hoffman, 1882	7.36 to 7.76	5.01 to 5.28	2.08 to 2.72	
Mya Viglezio, 1888	8.15	5.72	2.43	
Limbeck and Piek, 1893	6.5 to 7.4	3.82 to 3.83	1.58 to 1.97	
von Jaksch, 1893	8.44 to 9.19			
Lewinski, 1903	6.7 to 7.6			
Erben, 1905	8.5	3.85 to 5.38	2.48 to 3.78	
Reisz, 1902, 1912	7 to 9			
Strauss and Chajes	7 to 8.7			
Engel	7.4 to 9.4			
Martius	7.0 to 9.3			
Goldammer	6.6 to 9.1			
Bohme	6.8 to 8.9			
Widal, Benard and Vaucher	7.6 to 8.4			
Winternitz, 1908	5.11 to 5.68	3.92 to 4.01	1.19 to 1.67	0.17 to 0.24
Winternitz, 1910	7.8 to 8.49			0.46
Epstein, 1912	8.3	5.09	3.07	
Epstein, 1913	6.48 to 8.1	2.53 to 5.1	2.1 to 3.2	
Tranter and Rowe, 1915	6.7 to 8.7	4.95 to 7.7	1.2 to 2.54	
Rowe, 1916	6.5 to 8.2	1.6 to 6.7	1.2 to 2.3	
Epstein, 1917	7.4	4.66	2.73	
Loeper and Tonnet, 1919	7.8 to 8.0			
Dienst, 1918	7.17			
Zangemeister, 1919	7.78			
Kahn, 1920	6.76 to 8.47	4.39 to 5.43	2.23 to 3.21	
Epstein, 1922	6.0 to 8.0			
Rusznjak, Barit and Kurthy, 1924		3.25 to 4.39	1.25 to 2.07	0.12 to 0.24
Sehndera, 1924		4.2 to 6.8	1.3 to 3.5	0.1 to 0.26
Lander, Lundsgaard and van Slyke, 1924	6.22 to 7.45	3.36 to 4.9	2.26 to 2.89	
Lah and Swanson, 1926	7.2	4.9	2.3	0.3
Myers, 1924	6.5 to 8.2	4.6 to 6.7	1.2 to 2.3	
Iewin, 1927				
Silvesen, 1927	6.53 to 7.96	3.95 to 5.24	1.96 to 3.16	
Kollert and Starlinger, 1922	7.0 to 9.0			0.13 to 0.3
Stahlberg, 1928	7.8 to 8.1			
Kaptein, 1928				
Floyd and Paul, 1928				
Starlinger and Winands, 1928	6.93 to 9.13	4.21 to 5.78	1.41 to 4.03	0.36
von Farkas, 1928	6.1 to 8.7	3.6 to 5.5	1.4 to 3.9	0.2 to 0.3
Jones, 1929	5.86 to 8.42	4.12 to 6.1	1.05 to 2.96	0.18 to 0.3
Munk, 1929	6.9 to 7.8	4.4 to 5	2.1 to 2.8	
Winternitz, 1909				0.39 to 0.6
Pfeiffer, 1897				0.31 to 0.75
Lester, 1922				0.25 to 0.4
Gram, 1923				0.38, 0.2 to 2
Foster, 1924				0.3, \pm 5

* Quoted by Rowe

± 0.23 per cent. Chuay and Demanche, however, stated that the results secured by these two methods differed all the way from 1 to 17 per cent. In a later paper, Reisz admitted Schoei's corrections. Sources of error due to changes in the albumin-globulin ratio are, however, greatly reduced by Robertson's technique. A comparison of his results with

results secured by the direct method showed a variation of ± 0.2 per cent in the albumin value and of ± 0.15 per cent in the globulin value

Table 1, which embodies all the available data on the protein contents of normal serum, demonstrates that the values for total protein obtained by different investigators are fairly uniform. The albumin and globulin values, on the contrary, show marked variations, no doubt dependent on the different salts used in the salting out process. The same variation was found by Geill in his review (1927).

Personal Observations—The results of a series of combined analyses on the serums of eight normal males are given in table 2. Blood was taken from one of the veins in the antecubital fossa. With one exception (F. H. case 5), none of the subjects had taken food for at least twelve hours. The blood was allowed to clot and the serum was used at once for analysis.

TABLE 2—*The Proteins of Normal Serum (Personal Observations)*

Case	Total Protein, per Cent		Albumin, per Cent		Globulin, per Cent		A/G Ratio		Non protein Constit- uents	Non protein Nitro- gen
	Refrac- tometer	Kjel- dahl	Refrac- tometer	Kjel- dahl	Refrac- tometer	Kjel- dahl	Refrac- tometer	Kjel- dahl		
1	7.78	7.51	4.86	4.20	2.92	3.31	1.66	1.27	1.42	37.5
2	7.46	6.65	5.81	4.89	1.65	1.76	3.50	2.70	1.52	30.5
3	7.37	6.91	5.45	5.18	1.92	1.75	2.84	2.99	1.72	35.7
4	7.06		4.74		2.31		2.00		1.43	
5	7.33	7.54	4.83	4.68	2.50	2.86	1.93	1.60	1.80	42.9*
6	7.13	7.25	5.10	4.88	2.03	2.37	2.50	2.06	1.50	30.5
7	7.58	7.27	5.93	5.44	1.65	1.83	3.50	2.07	1.40	27.6
8	7.18	7.04	4.80	4.49	2.29	2.55	2.14	1.76	1.60	27.3
Max	7.78	7.54	5.93	5.44	2.92	3.31	3.50	2.99	1.80	42.9*
Min	7.06	6.65	4.86	4.20	1.65	1.73	1.66	1.27	1.40	27.3
Aver	7.36	7.17	5.20	4.82	2.16	2.34	2.52	2.10	1.51	33.1

* After a meal

The total protein values as determined by the two methods were rather uniform. In six of the eight cases, the refractometric value exceeded that found by the Kjeldahl method. The differences range from -0.12 to $+0.81$ Gm per hundred cubic centimeters. The greatest variations were found in the albumin-globulin ratios. The maximum difference here was 0.83 per cent. The average value of the non-protein constituents of the blood was also a little higher than that found by Tiantel and Rowe (1.5 as compared with 1.1 and 1.3 of Tiantel and Rowe).

THE PROTEINS OF SERUM AND PLASMA IN RENAL DISEASES

Observations in the Literature—The reported cases of changes in serum and plasma proteins in renal diseases have been arranged in five groups, and the results are given in tables 3 to 5. The grouping is

often uncertain, since many authors use the old terminology but it is the best that can be done with the available data

Group 1, Acute and Subacute Glomerulonephritis (table 3) The results in this group were fairly uniform. Seven of the ten investigators reported a moderate reduction of albumin and of total protein with normal or slightly increased globulin. The albumin-globulin ratio was lowered and at times reversed. In many cases there appeared to be a correlation between the amount of edema and the lowering of the total serum protein. This was, however, by no means constant. Similar observations were reported by Geill in his review (1927)

TABLE 3—*The Proteins of Serum and Plasma in Acute and Subacute Glomerulonephritis (from the Literature)*

Investigator	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent	A/G Ratio	Nonprotein Constituents	Fibrin, per Cent
Erben, 1905	Slight reduction					
Reisz, 1911	Reduced \pm					
Rowe, 1916	52 to 70	31 to 36	21 to 34		15 to 16	
Kahn, 1920	58.6 to 79.6	6.2 to 4.37	2.24 to 3.8		Normal	
Weltmann and Neumayer, 1925						Increased
Lahr and Swanson, 1926	41 to 84	16 to 5.2	16 to 3.6	0.45 to 2		0.3 to 1
Kollert and Starlinger, 1922			Normal			Increased
Müller, McIntosh and van Slyke, 1927		1.38 to 2.98	2.55 to 2.82	0.51 to 1.06		
Schwartz and Kohn, 1922	42 to 71.5					
J. Munk, 1929	Variable	Reduced	Increased	Reversed		

Erben and Reisz found a normal, or at most, a slightly reduced total protein and Kahn was unable to show any appreciable variation in the albumin, globulin or total protein values. In some of J. Munk's cases there were total protein values of 9 per cent or more. Reisz, however, pointed out that there was a slight reduction in serum protein in cases that showed edema. A consistent increase in fibrinogen has been reported but the number of analyses is too small to be of much value.

Group 2, Chronic Nephritis (a) Chronic nephritis with contraction (this includes both chronic glomerulonephritis and hypertensive contracted kidney) (table 4). In most instances, the values for serum proteins were normal or but slightly altered late in the disease. Kahn found normal values in all his cases. Edema tended to give the same picture as in acute and subacute nephritis, that is a lowering of the albumin and total protein with an occasional increase in the globulin. On the whole, however, the changes were much less marked and the correlation between edema and lower serum protein much less evident.

than in acute nephritis. These observations are in accord with those of Reisz, Rowe, Linder, Lundsgaard and Van Slyke, Starlinger and Winands, Fahn and Swanson, and Geill. Occasional exceptions can be found in table 4.

(b) Chronic parenchymatous nephritis. This group includes what is now called lipid nephrosis, both the pure and the mixed types (table 5). These cases showed the greatest quantitative changes in the serum proteins. With few exceptions there was a marked reduc-

TABLE 4—*The Proteins of Serum and Plasma in Chronic Nephritis with Contraction (from the Literature)*

Investigator	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent	A/G Ratio	Fibrin, per Cent
Bleibtreu, 1893	6.3 to 8.3			Normal	
Limbeck and Piek, 1893					
Limbeck and Piek, 1894	7.08 to 8.33				
Erben, 1903	Normal				
Reisz, 1913	Reduced \pm				
Epstein, 1914	7.09 to 7.52	2.31 to 4.98	2.5 to 4.77	0.48 to 1.9	
Epstein, 1917	6.70	4.31	2.39	1.8	
Reisz, 1914	6.65 to 8.72				
Rowe, 1917	3.8 to 5.1	1.9 to 3.9	1.1 to 2.0	No reversal	
Rowe, 1917	Normal	3.3 to 6.0	1.9 to 2.6	Slight reduction	
Rowe, 1917	5.8 to 7.9				
Rowe, 1917	6.1 to 7.9	3.6 to 6.1	1.8 to 2.5	Slight reduction	
Kahn, 1920	6.52 to 8.67	3.88 to 4.80	2.62 to 3.78	Normal	
Linder, Lundsgaard and van Slyke, 1924	Normal	Normal	Normal	Normal	
Weltmann and Neumayer, 1925					Increased
Rigler and Rybins, 1924	6.0 to 8.0	3.5 to 5.0	2.0 to 3.0		
Von Farkas, 1925			Increased	1.8 to 2.0	
Von Farkas, 1925			Normal	2.0 to 2.9	
Lahr and Swanson, 1926	4.9 to 7.7	1.8 to 5.1	2.3 to 3.5	0.5 to 2.0	0.3 to 1.3
Kollert and Starlinger, 1922			Normal		High normal
Hiller, McIntosh and van Slyke, 1927		1.77 to 3.48	1.64 to 3.64	0.62 to 1.34	
Starlinger and Winands, 1928	4.82 to 8.48	1.5 to 4.03	1.65 to 5.56	Lowered, reversed	Increased
Starlinger, 1928	1.82 to 8.48	1.5 to 1.0*	1.65 to 5.56	Lowered, reversed	Increased
Jones, 1929	6.81 to 8.69	3.81 to 5.50	1.54 to 3.18	1.42 to 3.57	0.29 to 0.82

tion in total protein. One of the cases reported by Fahn and Swanson showed a total protein of 3.4 Gm per hundred cubic centimeters. A similar decrease was found in the albumin fraction. The lowest albumin value (0.63 Gm per hundred cubic centimeters) was reported by Linder, Lundsgaard and Van Slyke in one of their cases of true nephrosis. In general the globulin fraction in the cases showed a pronounced increase, and the albumin-globulin ratio was always greatly lowered and usually reversed. In most of the cases, edema was present at some time or other, and in a general way there was a relation between the visible edema and the lower concentration of protein.

Several exceptions to the foregoing observations are encountered. Erben found the total serum protein within normal limits, but there was a distinct lowering and at times a reversal, of the albumin-globulin

ratio Kahn found no change in any of the protein fractions. Salvesen's case showed high serum protein (8.97 and 10.73 per cent) marked reduction in albumin (1.69 and 2.56 per cent), and striking increase in globulin (from 7.1 to 8.82 per cent). This patient never had edema.

TABLE 5—*The Proteins of Serum and Plasma in Chronic Parenchymatous Nephritis (Lipoid Nephrosis, Both the Pure and the Mixed Types (From the Literature))*

Investigator	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent	A/G Ratio	Fibrin, per Cent
Frben, 1905	7.81 to 7.89*	1.92 to 4.76	3.06 to 5.89	0.3 to 1.5	
Epstein, 1912	Reduced	Reduced	25% Increased	Reverse	
Epstein, 1917	3.92	0.46	3.46	0.13	
Epstein, 1922	3.92s	0.446	3.426	0.13	
Vollhard, 1918	Decreased				
Kahn, 1920	6.40 to 7.85	4.16 to 4.32	2.24 to 3.20	Normal	
Vandorfy, 1921	Decreased				
Kollert and Starlinger, 1922	5.61 to 6.85*	Decreased	Increased	Lowered	0.8 to 1.0
Rabinowitch and Childs, 1923	3.6 to 5.8	1.3 to 2.88	2.6 to 2.98	Reverse	
Kollert, 1923	Decreased			Lowered	Increased
Linder, Lundsgaard and van Slyke, 1924	3.55 to 7.82	1.6 to 4.8	1.5 to 3.76	0.6 to 2.0	
Linder, Lundsgaard and van Slyke, 1924	3.6 to 7.76	0.63 to 4.82	2.24 to 3.47	0.26 to 1.64	
Weltmann and Neumayer, 1925					Increased
Rigler and Rypins, 1924	6.1 to 7.22	2.19 to 3.08	3.39 to 5.0*	0.4 to 0.9	
Von Farkas, 1925			Increased	0.8 to 1.2	
Kisch, 1922		Low			
Munk, 1925			Increased		
Kaufmann, 1925	3.48 to 6.1	1.20 to 3.48	1.44 to 3.61	0.35 to 2.1	
Govaerts, 1926				Low	
Brunetti and Elek, 1925					Increased
Fahr and Swanson, 1926	3.4 to 5.0	1.8 to 2.8	1.4 to 3.3	0.5 to 2.0	0.2 to 0.7
Murphy and Warfield, 1926				Reversed	
Klimesch and Weltmann, 1927					Normal
Kollert and Starlinger, 1922					Increased
Elwyn, 1926	Reduced	Reduced	Normal		
Mason, 1926	3.48 to 7.39	Reduced	Increased		
Hiller, McIntosh and van Slyke, 1927			Variable	Reversed ±	
Salvesen, 1927	8.97 to 10.73	1.02 to 2.4	2.04 to 3.37	0.34 to 1.18	
Bannick and Keith, 1928	3.9 to 6.2	1.69 to 2.56	7.1 to 8.82	0.23 to 0.29	0.32†
Schultz, Swanson and Zeigler, 1928	3.61 to 5.42	0.98 to 3.22	0.63 to 3.25	Lowered and reversed	
Rachmilewitz, 1929	5.38 to 6	2.91 to 3.7	2.3 to 2.97	0.9 to 1.6	
Elwyn, 1930	Reduced	Reduced	Increased		
Geill, 1928	Reduced	Reduced	Normal		

* Refractometer

† This case showed no edema

Group 3, Amyloid Disease of the Kidney. The number of serum protein analyses recorded for this type of renal disease is too small to be conclusive. The few analyses that have been made indicate that the total protein and the albumin in these cases were reduced, and that the globulin was moderately increased (Reisz, Rigler and Rypins, Kisch, Silver and Lindbloom, Elwyn).

Group 4, Hypertensive Contracted Kidney. In practically all instances, the serum protein values were within normal limits (Linder, Lundsgaard and Van Slyke). Von Farkas reported a slight increase in globulin. In none of the cases was there edema.

Group 5, Renal Disease with Uremia Cases of renal disease with uremia, but without edema, showed normal serum proteins. The uremia, by itself, produced no alteration in the albumin-globulin fractions (Reisz, Rowe, Kollert and Starlinger).

Summary A review of the literature on the quantitative alterations in serum and plasma proteins in renal disease shows that the most striking changes were found in cases of chronic parenchymatous nephritis (lipoid nephrosis of the pure and mixed types). Here there was a marked reduction in the albumin and total protein with a high normal or a greatly increased globulin and a high percentage of reversals in the albumin-globulin ratio. The same series of changes, although less marked, were observed in acute and subacute glomerulonephritis. In chronic glomerulonephritis with contraction normal serum protein values were frequently found, and alterations, when they were encountered, never reached the magnitude of those in lipoid nephrosis. The fibrin values were usually increased, but, aside from the suggestion of Kollert, no particular attention was ever called to this fact. He associated edema with high fibrin values. This will be discussed later.

Personal Observations—Thirty-six cases of renal disease have been studied. These are classified as follows:

- 1 Acute glomerulonephritis, thirteen cases
- 2 Subacute glomerulonephritis, no cases
- 3 Chronic glomerulonephritis, twelve cases
 - (a) Chronic glomerulonephritis with contraction with nitrogen retention
 - (b) Chronic glomerulonephritis with contraction without nitrogen retention
 - (c) Lipoid nephrosis, pure and mixed types, one case
- 4 Amyloid kidney, two cases
- 5 Hypertensive kidney (primary contracted kidney) seven cases
- 6 Mercuric chloride nephrosis, one case

Group 1, Acute Glomerulonephritis Seventeen analyses were made in thirteen cases (table 6). With two exceptions (cases 5 and 6), the total protein values were lowered. The albumin was generally below normal, falling as low as 1.07 per cent, while the globulin showed a tendency to rise, at one time going to 4.42 per cent. The albumin-globulin ratio was frequently reversed (nine reversals in seventeen analyses). Normal ratios were, however, found in cases 2 and 3. There was a uniform tendency for the nonprotein constituents (determined by the refractometer, the technic of Robertson being followed) to rise the highest value observed being 2.3 per cent (normal 1.5 per cent).

A low total serum protein and a reversal of the albumin-globulin ratio did not always go together. At times the total protein was reduced while the albumin-globulin ratio remained within normal limits (case 2). Conversely, the total protein in one case (case 5) was normal while the albumin-globulin ratio was reversed.

TABLE 6—*The Proteins of Serum in Acute Glomerulonephritis (Personal Observations)*

Case	Total Protein, per Cent		Albumin, per Cent		Globulin, per Cent		A G Ratio		Fibrin, per Cent	Non protein Nitrogen, mg per 100 Cc		Urea Nitrogen, mg per 100 Cc	P S P *	Blood Pressure	Albuminuria	Comment
	Refrac tometer	Kjel dahl	Refrac tometer	Kjel dahl	Refrac tometer	Kjel dahl	Refrac tometer	Kjel dahl		Constit uents	Protein					
1	6.56		2.20		4.36		0.1			36.4		21.46	85	94/72	—	Recovering
2	7.60	5.62	4.14	4.22	1.46	1.40	2.8	3.0		1.5	37.5	18.66	70	118/82	Trace	Recovering
3	7.84		4.85		1.26		3.6			1.5		34.5	47	110/85	Trace	Recovering
4	5.14	5.79	2.20	2.75	3.24	3.04	0.7	0.9		2.3	240.0	119.7	1	210/140	++ +	Uremia
5	7.78	7.00	3.16	3.00	4.42	4.00	0.7	0.7		2.6	184.0	79.3	10	176/82	++	Post mortem
6	8.90		1.95		6.95		0.7			32.2		24.26	85	130/80	Trace	Recovering
7	5.40		3.29		2.20		1.5			1.1		34.6	32	126/78	++	At height of attack
	5.93		3.57		2.36		1.5			1.5		17.5	40		+	Recovering
8	6.62		3.92		2.70		1.5			1.6		62.3	28	160/100	++	At height of attack
	6.62		3.97		2.65		1.5			1.6		37.3	38		+	Recovering
9	4.97	3.37	1.57	1.54	3.40	1.83	0.5	0.8	0.1	1.5	60.5	35.0	50	100/110	++ +	At height of attack
	4.96	4.46	1.07	1.23	3.29	3.23	0.3	0.6	0.9	1.5	39.0	24.0			++	Recovering
	5.19	5.16	1.3	2.71	2.16	2.45	1.5	1.1		1.5	30.0	13.3	56	155/80	+	Recovering
10	5.89		3.66		2.23		1.64			2.02		7.9	?	90/65	++ +	Recovering
11	6.99	5.23	3.40	2.44	3.59	2.79	0.94	0.64		1.5		14.0	?	110/69	++ +	Recovering
12	1.92		1.63		2.69		0.64			1.46		11.0	38	140/90	++ +	Recovering
13	1.78		1.95		2.63		0.74			1.4						At height of attack
Mean	7.78	8.90	4.85	4.22	4.42	4.36	3.6	3.0	0.39	2.6						
Min	1.92	3.37	1.63	1.23	1.26	1.40	0.3	0.3	0.10	1.4						
Ave	5.67	5.68	3.05	2.45	2.67	3.44	1.34	0.95	0.25	1.65	82.5					

* P S P = phenolsulphonphthalein

TABLE 7—The Proteins of Serum in Chronic Glomerulonephritis

Case	Total Protein, per Cent		Albumin, per Cent		Globulin, per Cent		A/G Ratio		Ibrium, per Cent	Non protein Nitrogen, Mg per 100 Cc		Urea Nitrogen, Mg per 100 Cc	P S P	Blood Pressure	Albuminuria	Comment
	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl								
(a) Chronic Glomerulonephritis with Nitrogen Retention																
14	6.51	3.85	2.69	1.4	0.18	1.6	1.4	0.18	1.6	++	38.7	1	180/135	++		At height of attack
15	4.68	2.24	2.44	0.9		1.5	0.9		1.5	++	42.0	?	185/130	++		At height of attack
16†	1.70	2.37	2.33	1.0		1.5	1.0		1.5	+	26.0	?	112/112	++		Slight improvement
17	6.22	3.51	2.81	1.2	1.6	2.2	1.2	1.6	2.2	97.8	++	?	210/110	++		Uremia
18	5.27	3.64	1.63	2.2	2.9	1.6	2.2	2.9	1.6	51.7	++	?	108/120	+		At height of attack
19	4.55	1.66	1.19	2.31	0.68	1.5	0.52	0.68	1.5	57.0	++	6	114/81	++		Marked edema
20	5.07	2.76	3.21	0.86		1.5	0.86		1.5	—	—	1	111/81	+		Just before uremia
21	4.96	1.17	3.79	0.71	0.28	1.17	0.71	0.28	1.17	49.5	++	65	170/116	++		Slight improvement
22	5.83	1.70	4.13	1.01	0.22	2.13	1.01	0.22	2.13	173.3	—	38	190/110	++		Post mortem
23	5.11	2.91	2.70	2.65	1.1	1.5	1.2	1.1	1.5	39.8	—	45	186/104	+		Recovering
24	5.11	2.11	3.83	3.12	0.8	1.6	0.6	0.8	1.6	71.1	—	48	120/80	+		At height of attack
25	7.65	4.25	3.40	2.21	1.1	1.9	1.1	1.9	1.9	64.1	—	67	120/80	—		Recovering
26	5.22	1.71	3.51	3.27	0.5	1.6	0.5	0.5	1.6	111.3	—	1		++		Death in uremia
Max	7.65	6.61	4.13	4.46	2.2	2.2	2.2	2.9	2.2	173.3						
Min	4.68	3.93	1.63	1.71	0.1	1.17	0.1	0.22	1.17	39.8						
Avg	5.60	3.05	2.99	2.67	0.96	1.64	0.96	1.09	0.61	82.9						
(b) Chronic Glomerulonephritis Without Nitrogen Retention																
23	3.91	2.22	1.72	1		1.3	1		1.3	++	12.5	46	178/96	++		At height of attack
24	5.19	2.66	2.51	1.1		1.1	1.1		1.1	++	12.55	69	118/88	+		Improving
25	6.15	1.76	1.67	3.5		1.1	3.5		1.1	—	6.9	48	178/92	++		Some improvement
26	6.61	1.47	2.17	2.28	2.0	1.6	2.0	1.2	1.6	—	6.5	50		++		Some improvement
(c) A Case of Pure Lipoid Nephrosis																
25	5.24	1.06	1.18	3.30	0.23	1.88	0.23	0.31	1.88	++	8.1	65	Normal	++		At height of attack
	1.79	1.15	3.61	3.61	0.31	31.5	0.31	0.31	31.5	++	10.1	65	Normal	++		At height of attack
	3.79	1.72	2.67	2.67	0.8	39.7	0.8	0.8	39.7	+	9.0	65	Normal	++		Improving
	5.93	1.02	1.18	2.81	0.19	35.5	0.19	0.11	35.5	—	8.8	65	Normal	++		Improving

† Diagnosis confirmed post mortem

Group 2, Chronic Glomerulonephritis The cases of chronic glomerulonephritis are arranged in three groups (table 7) (*a*) those with definite nitrogen retention (*b*) those without nitrogen retention, and (*c*) one case of pure lipid nephrosis

In the cases of chronic glomerulonephritis with retention, the total protein was moderately reduced, the albumin was lowered, and the globulin was increased Several extremes are listed in the table In case 19, the total protein was 3.44 per cent, the albumin, 0.74 per cent, and the globulin, 4.46 per cent, on a second analysis In case 21 the total protein returned to normal while the patient was improving

The albumin-globulin ratio was lowered in all cases and reversed in six of the thirteen analyses The nonprotein constituents (as determined by the refractometer) were slightly increased

The two cases of chronic glomerulonephritis without retention showed essentially the same changes as those with retention In one analysis, however, the albumin-globulin ratio reached a high normal value (case 24) In all determinations, the nonprotein constituents (refractometer) fell a little below normal

The case of lipid nephrosis showed at times a marked reduction in the total protein and in albumin and a pronounced increase in globulin The albumin-globulin ratio was consistently reversed This picture is, however, practically the same as that in case 19 (chronic glomerulonephritis with retention)

The development of uremia in no way altered the serum proteins The nonprotein constituents were, however, increased

The unusually high nonprotein nitrogen value (173 mg per hundred cubic centimeters) recorded in the second analysis in case 19 requires some explanation This was determined on postmortem blood and as Ikeda and Jacoby have shown, the nonprotein nitrogen, especially the urea nitrogen rises rapidly after death

Group 3, Amyloid Kidneys (table 8) The changes in the serum proteins in the two cases of advanced renal amyloidosis are recorded in table 8 Both patients died in uremia No conclusions can be drawn from so small a number of cases, but the unusually low total protein (2.16 per cent) and albumin (0.2 per cent) values are to be noted There was an associated massive edema The analysis of the edema fluid is included in table 8

Group 4, Hypertensive Kidney With Renal Insufficiency (table 9) In six of seven cases of hypertensive renal disease with uremia the serum proteins were normal except for an occasional slight reduction of the albumin and total protein In case 31, however there was a moderate reduction of total proteins and albumin, with a reversal of the albumin-globulin ratio There was also an unusual rise in the nonprotein value (4.62 per cent) In this case there was a slight edema

TABLE 8—*The Proteins of Serum in Renal Amyloidosis with Uremia (Personal Observations)*

Case	Total Protein, per Cent		Albumin, per Cent		Globulin, per Cent		A/G Ratio		Non protein Constituents	Non protein Nitrogen, Mg per 100 Cc	Urea Nitrogen, Mg per 100 Cc	P S P	Blood Pressure	Albuminuria
	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl						
26	5.78		3.08		2.70		1.14		2.01		111.05	9	101/50	++
27														
Serum	2.16	2.87	0.20	0.32	1.96	2.55	0.1	0.12	1.5	78.1			111+	
Pleural fluid	0.160	0.063	?	0.06	?	0	0		1.2	47.6				

TABLE 9—*The Proteins of Serum in Cases of Hypertensive Kidney with Renal Insufficiency (Personal Observations)*

Case	Total Protein, per Cent		Albumin, per Cent		Globulin, per Cent		A/G Ratio		Non protein Constituents	Non protein Nitrogen, Mg per 100 Cc	Urea Nitrogen, Mg per 100 Cc	P S P	Blood Pressure	Albuminuria	Edema	Comment
	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl								
29	6.22		1.14		2.08		1.99		1.84		34.8	26	205/115	++	+	Three days before death
30	6.08		1.08		2.00		2.00		1.53		40.0		280/110	+	+	Early renal insufficiency
31	7.13		5.97		1.16		5.11		2.56		86.0		200+	+	—	Two days before death
32	5.78		2.64		3.14		0.84		1.62		145.0		210/100	+	+	Two days before death
33	6.27	6.63	4.11	4.13	2.16	2.50	1.8	1.6	2.15	209.8	10.1	5	200/110	++	+	Post mortem
34	7.37		4.61		2.76		1.67		1.67		12.0	1	250/140	+	+	Early uremia
35	5.97		4.52		1.45		3.12		1.57	91.6		0	138/68	Trace	++	Decompensated
Max	7.37		5.97		3.14		5.11		1.62	209.8						
Min	6.08		2.64		1.16		0.84		1.53	93.6						
Aver	6.10		4.29		2.11		2.37		2.28	151.7						

but this was no more pronounced than that found in cases with normal protein

Group 5, Mercuric Chloride Nephrosis (table 10) The single case of bichloride nephrosis included in this series showed a slight drop in albumin and total protein, with some increase in globulin. The albumin-globulin ratio was somewhat lowered, but not reversed. Edema was never observed, and the amount of protein lost in the urine was not great.

Summary In general, the same series of changes in the serum proteins were found in acute and chronic glomerulonephritis, lipid nephrosis, amyloid disease of the kidney and mercuric chloride nephrosis. The usual picture was a lowering of total protein and of albumin and an increase in globulin, with a lowered and at times reversed albumin-globulin ratio. The occasional exceptions have been pointed out.

TABLE 10—*Serum Proteins in Mercuric Chloride Nephrosis (Personal Observations)*

Case	Total Protein per Cent	Albumin, per Cent	Globulin, per Cent	A/G Ratio	Non protein Constituents	Edema	Urea Nitrogen 2Mg per 100 Ce	Albuminuria
36 { Serum	6.11	7.46	2.65	1.3	2.07	—	140	+
{ Urine	0.117	0.10	0.017	5.9	1.88			

* Determined by refractometer

In the cases of hypertensive kidney with renal insufficiency, practically normal serum proteins were found except in one case in which the total protein was moderately decreased and the albumin-globulin ratio reversed.

The nonprotein constituents (refractometer) were increased in all the types of renal disease considered, except in chronic glomerulonephritis without retention. The highest values were found in the cases of hypertensive kidney with renal insufficiency.

The fibrinogen values were always slightly increased.

THE PROTEINS OF SERUM AND PLASMA IN OTHER DISEASES

Lobar Pneumonia—Observations Recorded in Literature In cases reported in the literature (table 11), the serum and plasma protein showed definite changes. The total protein was generally lowered, only an occasional normal value being recorded. The albumin showed a consistent reduction, while the globulin and fibrinogen were usually increased. The albumin-globulin ratio was lowered, and reversals were frequently recorded.

Personal Observations Nineteen analyses in thirteen cases of lobar pneumonia are shown in table 12. With one exception, the total serum

TABLE 11—*The Proteins of Serum and Plasma in Lobar Pneumonia (from the Literature)*

Investigator	Total Protein, per Cent	Albumin, per Cent	Albumin, per Cent	A G Ratio	Fibrin, per Cent	Nonprotein Constituents
von Jaksch, 1893	7.25 to 11.63				Increased	
Limbeck and Piek, 1893		3.13	1.55			
Limbeck and Piek, 1894	5.05 to 6.39					
Pfeiffer, 1897					0.88	
Epstein, 1912	Lowered	Lowered	Increased	Low reversed		
Reisz, 1913	Lowered					
Reisz, 1914	5.69 to 6.89					
Schoeh,* 1916			Increased			
Mya Viglezio,† 1888		3.0 to 3.5	3.6 to 4.8			
Rowe, 1916	3.2	3.7	2.5	Lowered		1.4
Lester, 1922					0.73 to 1.45	
Gram, 1922					Increased	
Kollert and Starlinger, 1922	Lowered	Lowered	Increased	Lowered		
Schindera, 1924			Increased		Increased	
Foster, 1924			Increased		Increased	
Kollert, 1924	Lowered	Lowered	Increased		Increased	
Benedetti, 1924					Increased	
Weltmann and Neumayer, 1925					Increased	
McLester, Davidson and Frizler, 1925					Increased	
Iswin, 1927			Increased			
Klimesch and Weltmann, 1927					Increased	
Geill, 1927	Lowered	Lowered	Increased			
Stahlberg, 1928	Normal, lowered					
Starlinger and Winands, 1928	Normal lowered	Lowered	Increased	Reversed	Increased	
Berggrun *			Increased		Increased	
Halliburton *			Increased		Increased	
Starlinger, 1928			Increased		Increased	
Corbini, 1928				Low		
J. Munk, 1929	Lowered	Lowered	Increased	Low reversed		

* Quoted by Starlinger and Winands

† Quoted by Rowe

TABLE 12—*The Proteins of Serum in Lobar Pneumonia (Personal Observations)*

Case	Total Protein, per Cent		Albumin, per Cent		Globulin, per Cent		A G Ratio		Fibrin, per Cent	Albuminuria	Comment
	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl			
1	4.63	5.08	1.03	1.49	3.60	3.59	0.28	0.41	Trace	—	Just before crisis
	5.21	5.40	1.8	1.7	3.93	3.67	0.35	0.47	—	—	12 days after crisis
	5.96	5.28	2.89	1.88	3.07	3.40	0.94	0.57	—	—	17 days after crisis
	6.18	7.08	2.32	2.53	3.66	4.55	0.68	0.55	—	—	25 days after crisis
2	5.43	5.96	1.64	1.79	3.79	4.17	0.43	0.47	Trace	—	Just before crisis
	6.28	6.21	1.85	2.51	4.43	3.70	0.42	0.68	—	—	8 days after crisis
3	6.50	6.45	2.48	2.68	1.02	3.77	0.61	0.71	Trace	—	Just before crisis
	—	6.70	—	3.52	—	3.18	—	1.1	—	—	8 days after crisis
4	7.13	7.36	3.21	3.37	3.92	4.03	0.82	0.82	++	—	Just after the crisis
5	5.24		2.88		2.36		1.22		Trace	—	4 days after crisis
6	5.11		2.01				0.64		—	—	2 days before crisis
	5.65		2.90		2.75		1.05		—	—	8 days after crisis
7	5.52		2.08		3.44		0.60				Before crisis
8	6.0	5.74	3.91	3.68	2.22	2.06	1.7	1.8	0.999		3 days after crisis
9	6.24	5.73	2.72	2.19	3.57	3.54	0.77	0.60		Trace	During crisis
10	4.96		1.99		2.97		0.67			Trace	During crisis
11	5.65		3.38		2.27		1.5			Trace	5 days before crisis
12	5.56	4.45	2.59	1.31	2.97	3.14	0.87	0.41		Trace	2 days before crisis
13	6.01	5.02	3.15	1.90	2.86	3.12	1.1	0.6		Trace	2 days before crisis
Max	7.1	7.06	3.81	3.52	4.43	4.55	1.5	1.1			
Min	4.63	4.45	1.03	1.31	2.22	2.06	0.28	0.41			
Aver	5.74	5.88	2.47	2.35	3.28	3.53	0.81	0.70			

TABLE 13—*Changes in Serum and Plasma Proteins in Infections and Infectious Diseases (from the Literature)*

Investigator	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent	A G Ratio	Fibrin, per Cent	Disease
Bleibtreu, 1893	5.6 to 7.7					Pulmonary tuberculosis
Limbeck and Pick, 1894	9.17 to 9.65					Lumpyema
von Jaksch, 1893	8.25 to 9.3					Typhus
von Jaksch, 1893	8.27					Puerperal sepsis
von Jaksch, 1893	9.28					Rheumatic arthritis
Pfeiffer, 1897					0.31 to 0.75	Scarlet fever
Pfeiffer, 1897					0.17 to 0.43	Typhus
Pfeiffer, 1897					0.47 to 0.75	Erysipelas
Pfeiffer, 1897					0.62	Puerperal sepsis
Pfeiffer, 1897					0.56 to 0.88	Acute polyarthritis
Winternitz, 1908	4.79 to 7.21	2.93 to 4.11	1.86 to 2.63		0.33 to 0.49	Syphilis
Oppenheimer and Reisz, 1909	Lowered					Scarlet fever
Reisz, 1913	Lowered					Septicemia, arthritis
Reisz, 1914	7.75					Sepsis
Schoch,* 1916			Decreased			Acute polyarthritis
Rowe, 1916	6.4 to 8.8	3.7 to 5.7	2.7 to 3.4			Endocarditis
Rowe, 1916	7.5	5.4	1.9			Typhoid
Rowe, 1916	7.5	5	2.5			Syphilis
Alder, 1920			Increased, decreased			Tuberculosis
Frish, 1921					Increased	Tuberculosis
Lester, 1922					Increased	Septicemia
Lester, 1922					Increased	Tuberculosis
Gram, 1922					Increased	All infections
Rusznayk, Barat and Kurthy, 1924			Increased		Increased	All acute infections
Schindera, 1924		Decreased	Increased		Increased	All acute infections
Benedetti, 1924					Increased	All acute infections
Weltmann and Neumayer, 1925					Increased	All acute infections
McLester, Davidson and Frazier, 1925					Increased	All acute infections
Starlinger, 1925		Decreased	Increased			Syphilis
Lewin, 1927			Increased			All acute infections
Klimesch and Weltmann, 1927					Increased	All acute infections
Geill, 1927	Variable	Decreased	Increased			All acute infections
Wu †	8.0 to 9.4	Little change	Increased	Lowered		Syphilis
Wu †	6.8 to 10.5	Decreased	Increased	Reversed		Kala azar
Kaptein, 1928				Low reversed		Active tuberculosis
Starlinger and Winands, 1928	Lowered	Lowered	Increased	Low reversed	Increased	All acute infections
Berggrun *			Increased		Increased	Tuberculosis, polyarthritis
Halliburton *			Increased		Increased	Polyarthritis
Starlinger, 1928			Increased		Increased	All acute infections
Lloyd and Paul, 1928	7.9 to 10.17	Decreased	4.1 to 6.5	Low reversed		Kala azar
Corbin, 1928				Low		Tuberculosis
J. Munk, 1929	Normal, lowered	Decreased	Increased	Low reversed		influenza
J. Munk, 1929	Increased	Slight decrease	Increased	Reversed		All acute infections
Jones, 1929	7.54 to 8.71	4.07 to 4.86	2.27 to 3.99		0.41 to 0.79	Tuberculosis, infections

* Quoted by Starlinger and Winands

† Quoted by Geill

protein was moderately lowered, 4.96 per cent being the lowest value observed. There was a more striking reduction in the albumin, while the globulin showed a decided increase. Reversal of the albumin-globulin ratio was encountered in thirteen of the nineteen analyses. It was always present just before and during the crisis. Following the crisis, the total protein values rapidly increased, but the albumin and globulin values were much slower in returning to their normal levels. One case (1) observed for nearly one month after the crisis still showed a reversal of the albumin-globulin ratio. This may be partially explained by the fact that the patient showed a delayed resolution.

TABLE 14—*Serum Proteins in Acute Infections (Personal Observations)*

Case	Infection	Total Protein, per Cent		Albumin, per Cent		Globulin, per Cent		A/G Ratio		Albuminuria	Comment
		Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl		
1	Acute rheumatic fever	5.80	5.32	2.75	2.66	3.05	2.86	0.9	0.93	+	Temp 102-103 F
2	Pleurisy with effusion	5.59	5.61	2.96	2.86	2.63	2.75	1.1	1.0+	+	Temp 103 F
3	Chronic salpingitis	7.41		4.55		2.86		1.59		—	Temp 102-104 F
4	Typhoid fever	5.18	5.40	2.46	2.28	2.72	3.12	0.66	0.73	+++++	Pyelonephritis
5	Typhoid fever	6.67		3.67		3.00		1.2		—	Temp 104 F
6	Massive collapse of the lung	6.61	5.33	3.87	2.62	2.74	2.71	1.4	0.97	—	Temp 104 F
Maximum		7.41	5.61	4.45	2.86	3.05	3.12	1.59	1.0		
Minimum		5.18	4.33	2.46	2.28	2.63	2.71	0.66	0.73		
Average		6.21	5.47	3.34	2.60	4.17	2.91	1.14	0.90		

The urinary changes were generally insignificant. Most of the cases showed but a trace of albumin, or at most a + result just before and during the crisis, which disappeared immediately afterward. Case 4 was unusual in many ways. There were a heavy and persistent albuminuria, some casts and white blood cells and an occasional red blood cell. All this persisted for some time after the crisis, but finally subsided. The total serum protein was normal, but the albumin-globulin ratio was reversed. No doubt, the kidney was severely damaged.

Other Infections and Infectious Diseases—Observations Recorded in the Literature. In a miscellaneous group of cases of acute infections and infectious diseases collected from the literature (table 13), the values for total serum protein showed considerable variation. In some cases they were normal, in others moderately reduced, while in still others they showed an increase. The albumin values showed practically the same variations. The globulin and fibrinogen values on the other

hand, were consistently elevated. Albumin-globulin ratios were lowered and at times reversed.

Kala-azar (cases reported by Wu and Lloyd and Paul) showed exceptionally high total serum protein and globulin. The albumin was normal or moderately reduced, while the albumin-globulin ratio was low and reversed. Lloyd and Paul added that such serums had a higher hydrogen ion concentration and a lower iso-electric point than normal.

Personal Observations. In the miscellaneous group of acute infections (table 14), the serum protein changes were in general the same.

TABLE 15 —*The Proteins of Serum and Plasma in Heart Disease, With and Without Edema (from the Literature)*

Investigator	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent	A/G Ratio	Fibrin, per Cent	Edema
Von Jaksch, 1863	9.63					—
Reisz, 1913	Normal					—
Reisz, 1913	Lowered					+
Rowe, 1917	6.9 to 7.3	4.6 to 5.0	2.7 to 1.9			—
Rowe, 1917	6.0 to 1.3	3.4 to 4.7	1.9 to 3.2			+
Kahn, 1920	6.69 to 7.17	3.95 to 4.16	2.74 to 3.01			+
Lester, 1923					Slight increase	
Gram, 1922					Normal	
Weltmann and Neumayer, 1925					Normal	—
Weltmann and Neumayer, 1925					Increased	+
McLester, Davidson and Frazier, 1925					Increased	
Adler and Strausz, 1925			Decreased			
Fahr and Swanson, 1926	5.7 to 7.4	2.5 to 4.2	2.3 to 3.2	0.8 to 1.3	0.2 to 0.3	+
Govaerts, 1926				Lowered 0.36		
Von Farkas, 1926		Normal	Normal	Normal		—
Von Farkas, 1926			Increased	Lowered		+
Klimesch and Weltmann, 1927					Slight increase	
Geill, 1927	Lowered	Lowered	Increased			±
Von Farkas, 1928	Normal	Normal	Normal	Normal	Normal	—
Von Farkas, 1928	5.10 to 5.76	2.46 to 3.52	1.92 to 2.22	Lowered	0.32 to 0.58	+
Stalinger and Winands, 1928	Normal, lowered	Lowered, normal	Increased, normal	Lowered, reversed	Normal, increased	±
Jones, 1929	6.48	2.86	2.59		0.27	

as in lobar pneumonia, but less marked. With a single exception, the total protein was reduced, the albumin lowered and the globulin increased. The albumin-globulin ratio was consistently lowered and reversed twice (cases 1 and 4). The serum proteins were determined at the height of the infection. The urine showed no albumin or only a trace, except in case 4, in which there was a severe pyelonephritis. The blood urea nitrogen ranged from 153.5 to 207.6 mg. per hundred cubic centimeters.

Heart Disease, With and Without Edema.—Observations Recorded in the Literature. A survey of the literature (table 15) on heart disease both with and without edema shows that the changes in the values for the total serum protein, albumin and globulin were seldom marked. Rarely did these alterations reach the magnitude commonly encountered in some types of renal disease (Reisz, Rowe, Stalinger and Winands).

TABLE 16—Serum Proteins in Cardiac Decompensation with Edema (Personal Observations)

Case	Total Protein, per Cent			Albumin, per Cent		Globulin, per Cent		A G Ratio		Non protein Constituents	Non protein Nitrogen, Mg per 100 Cc	Edema	Urea Nitrogen, Mg per 100 Cc	Blood Pressure	Albuminuria	P S P	Decompensation
	Refractometer	Kjeldahl		Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl								
1	5.24		1.28	3.96		0.72		1.5				++++	26	190/135	Trace	?	Marked
2	5.37	6.76	3.97	1.76	2.50	2.3	1.5	1.3		37.3		++++	20	?	Trace	?	Marked
3	6.50	6.12	1.90	2.11	1.89	2.1	2.2	1.64		30.3		++++	?	175/110	—	?	Marked
4	6.75	6.63	2.66	3.69	3.84	0.72	0.72	1.69		38.8		++	18.4	232/116	—	46	Moderate
7*	5.65	5.74	2.23	3.02	2.47	0.87	1.16	1.51		145.6		++++	?	124/84	Trace	?	Marked, ++ jaundice
6	5.11	4.83	4.01	1.10	1.15	3.6	3.2	1.40		37.1		+	26	170/115	+	35	Marked
Max	6.50	6.63	4.30	3.69	3.94	3.6	3.2	1.69		115.6							
Min	5.11	4.83	1.28	1.10	1.15	0.72	0.72	1.3		30.3							
Aver	5.70	5.86	3.00	3.48	3.48	1.65	1.76	1.51		61.8							

* Diagnosis confirmed at autopsy

Cases without edema, ascites or hydrothorax generally showed normal values throughout. The presence of edema tended to produce a slight lowering in the albumin and total protein and at times a slight increase in globulin (Rowe, Starlinger and Winands). More marked changes were found in the cases of Fahn and Swanson, Govaerts, and von Farkas. These authors reported reversals of the albumin-globulin ratio.

Von Farkas gave the impression that there is a direct relationship between low albumin, low total protein, increased globulin and edema. No such correlation exists in some of the cases reported by Kahn, Fahn and Swanson, Starlinger and Winands, and von Jaksch. These authors frequently encountered normal and increased values in the presence of marked edema. Geill in his review (1927) concluded that there might be a slight increase in globulin in cases of decompensated heart, regardless of the presence or absence of edema.

The fibrinogen values were generally normal. Occasionally they showed a slight increase.

Personal Observations. In the six cases of cardiac decompensation with edema (table 16), the total serum protein showed a moderate reduction, never, however, falling below 5.11 per cent (refractometer) or 4.83 per cent (Kjeldahl). Four of the six cases displayed low albumin on one occasion as low as 1.28 per cent (case 1). The globulin, with one exception (case 6), was moderately increased. Reversals of the albumin-globulin ratio were found in three of the six cases.

No constant relationship could be established between low serum protein, reversal of the albumin-globulin ratio and edema. The first five of the six cases had practically the same degree of edema (4+), yet, as the table shows, the serum protein and the albumin-globulin ratios showed no similarity. Case 6, which showed the least edema (+), displayed the lowest total protein (4.83 per cent) and an albumin-globulin ratio of 3.2.

Renal function was fair and consistent with the degree of cardiac decompensation and congestion. The urines as a rule never showed more than an inconstant trace of albumin. In case 6 the urine at one time showed a value of 1+.

The total nonprotein values (refractometer) were slightly below normal.

Pregnancy and Eclampsia.—In the literature there is no agreement as to the level of the plasma proteins in normal pregnancy with edema and albuminuria (eclampsia and preeclampsia).

Personal Observations. In the five cases of preeclamptic toxemia, the serum protein values were all within normal limits (table 17). Several of the cases showed a slight decrease in total serum protein and in the albumin-globulin ratio. Edema and albuminuria produced no

direct change in the serum protein. The kidney was not severely damaged in any instance, and all the patients made a complete recovery. The nonprotein values (refractometer) were normal throughout.

Malnutrition and Starvation with Edema—Observations Recorded in the Literature. From a review of the literature, as well as from his original work, Mavei concluded that starvation edemas are due to a

TABLE 17—*The Proteins of Serum and Plasma in Pregnancy with Eclampsia (Personal Observations)*

Case	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent	A G Ratio	Non protein Constituents	Non protein Nitrogen, Mg per 100 Cc	Urea Nitrogen, Mg per 100 Cc	Blood Pressure	Edema	Albuminuria
1 (pre-eclampsia)	6.49	4.23	2.26	1.87	1.73	37.6	9.65	160/100	++	+++
2	6.76	4.50	2.26	1.99						
2 (pre-eclampsia)	7.65	4.93	2.72	1.81	1.45	39.2	10	155/112	—	++++
3 (pre-eclampsia)	6.78	4.91	1.87	2.62	1.19	?	17.7	140/90	+	++++
4 (pre-eclampsia)	7.73	4.32	3.41	1.26	1.5	28	12.1	154/116	++	—
5 (pre-eclampsia)	6.77	5.37	1.40	3.83	2	39	10	155/112	—	++++
Maximum	7.73	4.91	3.41	3.83	2	39.2	9.65			
Minimum	6.49	4.23	1.40	1.26	1.45	28	17.7			
Average	7.0	4.71	2.32	2.23	1.57	35.9	11.89			

* Determined by refractometer

TABLE 18—*The Proteins of Serum and Plasma in Deficiency and Dietary Edemas (Personal Observations)*

Case	Total Protein, per Cent		Albumin, per Cent		Globulin, per Cent		A G Ratio		Nonprotein Constituents	Nonprotein Nitrogen, Mfg per 100 Cc	Edema	Comment
	Refractometer		Refractometer		Refractometer		Refractometer					
	Kjeldahl		Kjeldahl		Kjeldahl		Kjeldahl					
1	3.36	4.19	0.66	0.76	2.70	3.43	0.19	0.22	4.25		++++	Dietary deficiency
	3.32		1.01		2.31		0.43		1.40		++++	Post mortem
2	6.23	6.62	4.00	4.25	2.23	2.37	1.79	1.79	1.84		++	No apparent cause
3		6.38		3.81		2.57		1.48		34.5	++	Dietary deficiency
4	4.22	4.08	2.64	1.94	1.58	2.14	1.67	0.90	1.45		++++	Starvation

diet low in protein and high in salt and water. Geill and Jansen found the serum protein greatly reduced in both malnutrition and starvation. Their cases were edematous. Jansen reported a case in which the serum protein fell to 4.03 per cent. J. Munk and Gorter found edema in children who were improperly fed and who were suffering from various types of digestive disorders. In J. Munk's cases, the total serum protein was normal or slightly reduced, the albumin usually reduced and the globulin generally increased. The albumin-globulin ratio was lowered and at times reversed. Bigland encountered edema in pellagra, beriberi, malaria and starvation.

Personal Observations. In three of the cases listed in table 18 there was a clear history of dietary deficiency or starvation. In case 2, how-

ever, an adequate cause was never found. The edema cleared up spontaneously, but recurred several times later.

The total serum protein was reduced, the values ranging from 3.32 to 6.62 per cent. The albumin was lowered, falling to 0.66 per cent in case 1. The globulin in all cases showed a uniform, moderate increase while the albumin-globulin ratio was lowered and definitely reversed in case 1. There was also a partial reversal in case 4 (value determined by Kjeldahl). Case 1 was unusual in that it showed the greatest edema, the lowest total serum protein, a pronounced reversal of the albumin-globulin ratio and a nonprotein value (refractometer) of 4.25 per cent.

Starvation and Marked Emaciation Without Edema—Personal Observations. By way of contrast, two cases of starvation with extreme emaciation, but without edema, are given (table 19). These patients took neither food nor water. Perhaps the lack of water was responsible

TABLE 19—*Serum Proteins in Starvation and Marked Emaciation Without Edema (Personal Observations)*

	Total Protein, per Cent		Albumin, per Cent		Globulin, per Cent		A/G Ratio		Non protein Con stitu ents	Comment
	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl		
1	6.18		4.00		2.18		1.8		1.1	No food or water
2	4.88		3.00		1.83		1.8		1.7	Marked emaciation, biliary fistula

for the absence of edema. This would be in accord with the experimental work of Fisch, Mendel and Peters, already cited.

The serum proteins showed essentially the same changes as in the deficiency and dietary edemas. The albumin-globulin ratio, although lowered, was never reversed.

Carcinoma—Observations Recorded in the Literature. Most of the reports in the literature on cases of malignant tumors, especially of carcinoma, show a slight lowering of the total serum protein and an increase in globulin. Loeper and Tonnet found the total serum protein low in the early stages of carcinoma, while later it sometimes became as high as 9.2 per cent. This late rise they attributed to a direct transformation of tumor tissue into serum protein. Corbin reported a total serum protein of 12.1 per cent. Loebner reported nearly normal total protein values in most of his cases (average, 7.3 per cent), but two with edema showed low values (4.2 and 4.4 per cent). The albumin was reduced and the globulin increased. Another of his cases without edema presented a total serum protein of 9 per cent.

Loebner further pointed out that although the globulin is usually increased this increase bears no relationship to the total protein figure.

The fibrinogen was slightly increased in all cases.

Personal Observations There was a striking lack of uniformity in the total protein values (table 20). They ranged from 3.33 to 7.19 per cent. The albumin was reduced in all cases, while the globulin was generally slightly increased, although it fell to 0.93 per cent in case 5. No relation existed between the serum protein values and the degree of edema or ascites. The total nonprotein values (refractometer), with one exception, were a little below normal. There was nothing to indicate serious damage to the kidney in any of the cases. Cases 4 and 5 showed a slight increase in nonprotein nitrogen in the blood and a trace of albumin in the urine. Both, however, were complicated by early stages of peritonitis.

In case 5, in addition to carcinoma of the stomach, marked emaciation was shown, but no edema. The patient had eaten little for about ten

TABLE 20—*Serum Proteins in Carcinoma and Sarcoma (Personal Observations)*

Case	Total Protein, per Cent		Albumin, per Cent		Globulin, per Cent		A/G Ratio		Nonprotein Constituents	Nonprotein Nitrogen, Mg per 100 Ce	Urea Nitrogen, Mg per 100 Ce	Albuminuria	Edema
	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl					
1 Carcinoma of groin	5.95	5.24	2.62	2.34	3.33	2.90	0.78	0.80	1.34	16.6	?	—	—
2 Carcinoma of ovary	7.19		3.77		3.32		1.13		1.15		?	—	+
3 Carcinoma of stomach	5.36		3.78		1.58		2.22		2.31		?	—	+
4 Sarcoma of stomach	5.74	5.86	3.87	3.56	1.87	2.30	2.07	1.55	1.34	60.0	?	Trace	—
5 Carcinoma of stomach		3.33		2.40		0.93		2.6		43.1	23.1	Trace	—
Maximum	7.19	5.86	3.87	3.56	3.33	2.90	2.32	2.6	2.31	60.0			
Minimum	5.36	3.33	2.62	2.34	1.58	0.93	0.78	0.80	1.15	18.6			
Average	6.06	4.81	3.51	2.77	2.53	2.04	1.58	1.65	1.54	40.9			

days before the serum proteins were determined, and this may account for a part of the unusual blood picture.

Lymphogranuloma and Leukemia—None of the cases of lymphogranuloma or leukemia reported in the literature showed marked or constant changes in the serum or plasma proteins. The values were generally within normal limits (von Jaksch, Eiben, Starlinger and Winands).

Personal Observations The serum proteins were normal in the case of lymphatic leukemia (table 21). In Hodgkin's disease the albumin and total protein values were moderately reduced. The patient had a slight edema of the feet and ankles. The urine was normal in both cases.

Multiple Myeloma—The unusual protein in multiple myeloma was first described by Bence-Jones in 1847 (quoted from Abderhalden). Its presence in the blood serum was described by Decastello, Krausz, and Short and Crawford. The exact amounts were, however, not recorded.

A series of quantitative analyses on serum proteins and Bence-Jones protein are recorded in table 22, taken for the most part from the paper of Bannick and Greene (1929). The total serum protein, albumin and globulin are all subject to great variation. The total protein varies from 5.27 to 13.15 per cent, albumin from 2.50 to 5.26 per cent, and globulin from 0.73 to 9.09 per cent. Jacobson isolated the Bence-Jones protein from the serum and found that it amounted to 7.86 per cent. Doubtless the high values for total serum protein and globulin are due to

TABLE 21—*Serum Proteins in Lymphatic Leukemia and Hodgkin's Disease (Personal Observations)*

Case	Total Protein, per Cent		Albumin, per Cent		Globulin, per Cent		A/G Ratio		Fibrin, per Cent	
	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl
1 Lymphatic leukemia	7.05		4.89		2.16		2.26		1.5	
2 Hodgkin's disease	5.86		4.27		1.59		2.68		1.5	+

TABLE 22—*Serum Proteins and Bence-Jones Protein in Multiple Myeloma (from the Literature)*

Investigator	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent	A/G Ratio	Bence Jones Protein, per Cent
Bannick and Greene, 1929	9.00	2.50	6.50	0.38	
Bannick and Greene, 1929	7.30				
Bannick and Greene, 1929	6.00				
Bannick and Greene, 1929	10.54	4.45	6.09	0.73	
Bannick and Greene, 1929	7.00	5.26	1.74	3.02	
Perlzweig, Delrue and Gischickler, 1928	13.54	4.06	9.09	0.45	
Jacobson, 1917					7.86
Rowe, 1917	6.80	4.8	2.0	2.40	
Hewitt, 1929	6.31	4.35	1.96	2.22	
Case, 1929	5.27	4.54	0.73	6.22	
Thannhauser and Krausz, 1920	6.41				
Taylor, Miller and Sweet, 1917					0.2

accumulation of the Bence-Jones protein. Taylor, Miller and Sweet reported a case in which the Bence-Jones protein in the serum amounted to only 0.2 per cent, while Weber, Hutchinson and Macleod found Bence-Jones protein in the urine, but the amount in the blood was too small to show by chemical analysis.

Observations in a Case of Multiple Myeloma Associated with Hyperproteinemia (table 23). The case presented the usual physical and roentgenologic signs of multiple myeloma. The urine contained only a trace of albumin and no Bence-Jones protein. Repeated analyses of the serum and plasma showed a striking elevation of total protein and

globulin, with a normal or slightly reduced albumin. The albumin-globulin ratio was consistently reversed. The fibrinogen was increased.

It would seem logical to assume, in the presence of the high globulin figures, that at least the greater part of the Bence-Jones protein had been carried down with the globulin. Some support is added to this assumption by the fact that after precipitating the globulin by half saturation with ammonium sulphate, the clear supernatant liquid failed to show a clouding when heated to 56 C.

TABLE 23—*The Proteins¹ of Serum and Plasma in Multiple Myeloma with Hyperproteinemia (Personal Observations)*

Case	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent	A/G Ratio	Nonprotein Constituents	Fibrin, per Cent
1 Serum	13.76	5.81	7.95	0.73	1.7	
1 Plasma	14.13	4.65	9.48	0.49	1.6	
1 Plasma	13.27	3.87	9.40	0.41	1.9	1.45

* Analysis by refractometer

TABLE 24—*Serum Proteins in a Group of Miscellaneous Diseases (Personal Observations)*

Case	Total Protein, per Cent		Albumin, per Cent		Globulin, per Cent		A/G Ratio		Nonprotein Constituents	Nonprotein Nitrogen, Mg per 100 Gc	Urea Nitrogen, Mg per 100 Gc	Albuminuria	Edema	Comment
	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl						
1*	6.88		5.51		1.37		4.02		1.97	214.0	107.1	++	—	Pyelonephritis, death in uremia
2	5.94		3.50		2.44		1.43		1.7		23.6	++++	—	Stone in the kidney
2	5.96		3.00		2.96		1.01		1.4		21.5	++++	—	
3	7.26	7.37	5.18	4.85	2.18	2.52	2.3	1.6	1.4	21.8	?	+	—	Lysol poisoning
4*	4.57		1.45		3.12		0.46		6.3			+	—	Acute atrophy of the liver
	6.71		3.15		3.56		0.88		2.6					Postmortem blood
5*	6.30	6.13	3.81	3.08	2.49	3.05	1.5	1.0	2.2	172.4	78.4	+	++	Pyelonephritis, uremia

* Diagnosis confirmed at autopsy

Diseases of the Liver—In cases of diseases of the liver, the total serum protein was normal or slightly reduced (Stallinger and Winands, Abram and Robert-Wallich, Gruet, Gilbert and Chuay). The albumin was usually reduced (Brunetti and Elek, Abram and Robert-Wallich, Stallinger and Winands), but occasionally increased (Rusznayak, Barát and Kurthy). The globulin was sometimes normal (Rusznayak, Barát and Kurthy, Brunetti and Elek, Stallinger and Winands), increased or decreased (Adler, McLester, Davidson and Frazier, Lewin, Stallinger and Winands, Rusznayak, Barát and

Kuithy Schindera, Adler and Strausz) The albumin-globulin ratio was low and frequently reversed (Starlinger and Winands) Fibrinogen showed both an increase and a decrease (McLester, Foster and Whipple, Gram, Isaak-Kiegei, Hiege, Scheffer, Weltmann and Neumayer, Benedetti, Klimesch and Weltmann)

Pyelonephritis and Renal Stone—The total serum protein was within normal limits, the albumin reduced and the globulin greatly increased The albumin-globulin ratio was low and at times reversed (Epstein) The changes in serum proteins were probably due to the infection

In the cases of pyelonephritis reported by Starlinger and Winands the total protein was normal, the globulin normal or slightly increased, and the albumin normal or slightly decreased The albumin-globulin ratio was normal for the most part, but showed a reversal on one analysis The fibrinogen was increased Corbin reported a case with renal stone in which the albumin-globulin ratio fell to 1.3

Personal Observations (table 24) With the exception of case 3 (lysol poisoning) in which the protein values were normal throughout, the total serum protein was lowered, the lowest value (4.57 per cent) being encountered in acute atrophy of the liver Three of the cases (nos. 2, 4 and 5) showed lowered albumin, increased globulin, a lowering of the albumin-globulin ratio and, in case 4 (acute atrophy of the liver), a pronounced reversal of the albumin-globulin ratio

PROTEINS IN EDEMA FLUIDS

A series of analyses on proteins in noninflammatory edema fluids (subcutaneous fluid and ascitic and pleural fluid) in nutritional disturbances, renal disease, cardiac decompensation and cirrhosis of the liver are given in table 25

The lowest total protein was found in "watery edema" (Jansen, table 25 [e]) The edema fluids of renal disease, cardiac decompensation and cirrhosis of the liver showed practically the same composition The values for total protein, albumin and globulin were all subject to considerable variation and were not characteristic of any particular disease Epstein pointed out that the protein content of the edema fluid varies both with the disease and with the location of the fluid He found the lowest amount of protein in subcutaneous fluids and the highest in pleural fluids, with the abdominal fluids occupying an intermediate position

In table 25 (a), it is shown that lower protein was found in the edema fluids of nephrosis and amyloid disease of the kidney than in nephritis (Hellmuth and Beckmann) Beckmann believed that cardiac and cachectic edemas occupy a position midway between those of

TABLE 25—*Proteins in Edema Fluids (from the Literature)*

Investigator	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent	A G Ratio	Type of Renal Disease and Fluid
<i>(a) Renal Disease with Edema</i>					
Jansen	0.578				Nephrosis
Beckmann	1.12 to 1.54				Glomerulonephritis
Beckmann	0.09				Nephrosis
Beckmann	0.03 to 0.16				Amyloid kidney
Beckmann	1.18				Acute glomerulonephritis
Pigeaud *				0.64 to 0.69	Nephritis, pleural fluid
Hellmuth	0.85 to 1.67				Glomerulonephritis
Epstein	0.098 to 0.17	0.018 to 0.066	0.079 to 0.104	0.24 to 0.84	Nephritis, anasarca fluid
Epstein	1.25 to 3.58	0.37 to 2.11	0.87 to 1.46		Nephritis, pleural fluid
Epstein	0.285		0.285		Nephritis, ascitic fluid
<i>(b) Cardiac Decompensation with Edema</i>					
Beckmann	0.25 to 1.54				
Paykull *		0.47 to 0.73	0.38 to 0.72		Ascitic fluid
Csartary		0.284	0.289	0.9	Ascitic fluid
Csartary		0.337	0.131	2.5	Pleural fluid
Epstein	0.1	0.82	0.018		Cardionephritis, anasarca fluid
Epstein	1.56 to 4.69	0.97 to 3.05	0.88 to 1.91		Ascitic fluid
<i>(c) Pregnancy and Eclampsia with Edema</i>					
Hellmuth	±0.14				
<i>(d) Cirrhosis of the Liver with Ascites</i>					
Jansen	0.856				
Abram and Robert Wallach	1.0 to 2.2	0.5 to 1.1	0.4 to 1.4		
Beckmann	0.21 to 0.35				
Joachim *	0.74 to 1.89				
Pigeaud *				1.41	
Paykull *		0.76 to 2.56	0.49 to 2.03		
Starlinger and Winands	3.32	1.71	1.61		
Epstein	0.52 to 3.33	0.19 to 2.00	0.32 to 1.61		
<i>(e) War (Nutritional) Edema</i>					
Jansen	0.078 to 0.063				

* Quoted by Starlinger and Winands

nephrosis and nephritis Csaitary thought that the transudation of serum protein, especially albumin, into the tissue fluids is directly related to the height of the blood pressure This was denied by Hellmuth and Eppinger

A correlation between the albumin-globulin ratio of edema fluids and that of serum was reported by Mya-Viglezio, Pigeaud, Csaitary

TABLE 26—*Proteins in Edema Fluids (Personal Observations)*

Case	Total Protein, per Cent		Albumin, per Cent		Globulin, per Cent		A/G Ratio		Nonprotein Constituents	Nonprotein Nitrogen, Mg per 100 Gc	Urea Nitrogen, Mg per 100 Gc	Disease and Kind of Fluid
	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl				
1	1.23 0.50 3.32		0.30 0.01 1.01		0.84 0.40 2.31		0.46 0.02 0.43		1.3 0.0 2.52	40.6	13.2 22.0	Starvation edema Peritoneal fluid Pleural fluid Serum
2	0.64 4.85	0.563 3.93	? 1.66	0.15 1.59	? 3.19	0.418 2.34	? 0.52	0.36 0.63	1.31 1.44	57.0 54.0		Chronic glomerulonephritis Ascitic fluid Serum
3	0.66		0.62		0.04		15.0		2.00			Chronic glomerulonephritis Ascitic fluid
4	0.16 2.16	0.063 2.87	? 0.20	0.063 0.82	? 1.96	— 2.55	0.1 0.12		1.22 1.7	47.6 53.1		Renal amyloidosis Pleural fluid Serum
5	3.63 6.27	4.22 6.63	2.67 4.11	2.46 4.13	1.16 2.16	1.76 2.50	2.38 1.8	1.4 1.6	2.00 2.15	201.0 209.0		Hypertensive kidney Ascitic fluid Serum
6	1.84 5.36		0.98 3.78		0.86 1.58		1.14 2.4		1.63 2.31			Metastatic carcinoma of the liver Ascitic fluid Serum
7	0.535	0.593	0.045	0.312	0.49	0.281	0.09	1.11	1.35	94.0		Mechanical edema, subcutaneous fluid
8	3.60		1.67		2.02		0.82		2.41			Cardiac decompensation, pleural fluid
9	2.52 5.73	2.87 6.36	1.45 3.97	1.07 3.86	1.07 1.76	1.80 2.50	1.3 2.3	0.5 1.5	1.3 1.6	30.0 37.0		Cardiac decompensation Ascitic fluid Serum
10	5.28		3.53		1.75		2.01		1.27			Cirrhosis of the liver Ascitic fluid

(nephritis) and Starlinger and Winands (cardiac edema) Epstein found a close relationship between the globulin percentage of the total protein in serum and that of edema fluids in nephritis This was not true in his cases of "cardionephritis" Hoffmann was unable to find any correlation between the protein values or ratios of serums and those of edema fluids

Denis and Minot found practically the same nonprotein values in serum and edema fluids. Epstein, however, found lower nonprotein nitrogen values in edema fluid than in serum.

Personal Observations. The results of a series of analyses on edema fluids with the serum protein values, when such were determined, are recorded in table 26. The lowest protein value of pleural fluid was found in a case of renal amyloidosis (0.063 per cent). All of this was albumin (Kjeldahl). The ascitic fluid in chronic nephritis showed a much higher value (0.568 per cent). This is in accord with the results recorded in the literature.

The protein content of the pleural fluid in the case of starvation edema was likewise low (0.5 per cent). Mechanical pressure on the iliac veins by a carcinoma in the pelvic cavity gave rise to an edema of the legs (case 7), the fluid of which was low in protein (0.535 per cent).

The edema (ascitic fluid) accompanying cardiac decompensation had a somewhat higher protein content (from 2.52 to 3.69 per cent).

The highest protein value was found in the ascitic fluid, associated with cirrhosis of the liver (5.28 per cent).

A fair correlation existed between the albumin-globulin ratio of the edema fluids and that of the serum. A reversal of the ratio in one was accompanied by a similar change in the other (cases 1 and 2) and vice versa (case 5). Case 9 was a partial exception. A similar correlation was found in the nonprotein nitrogen values of the edema fluid and the serum. The number of analyses was, however, much too small to justify conclusions.

It is significant that both in the cases listed in table 26 and in those recorded in the literature the edema fluid usually contained both albumin and globulin. Only once was the protein entirely albumin. Either one may predominate.

It appears that the capillaries are permeable to both albumin and globulin.

SUMMARY AND COMMENT

Summary of the Protein Changes in Disease.—Aside from the cases of hypertensive kidney, in which normal serum protein values were the rule, all forms of renal disease showed a reduction in total protein and albumin and an increase in globulin. The albumin-globulin ratio was usually lowered and frequently reversed. The quantitative protein changes in lipid nephrosis were no more marked than those found in some cases of chronic glomerulonephritis. Amyloid disease of the kidneys and mercuric chloride nephrosis showed essentially the same protein changes as were found in acute and chronic glomerulonephritis and in lipid nephrosis.

Much the same protein picture was found in acute infectious diseases, here also the total protein and albumin were reduced, the globulin was increased, and the albumin-globulin ratio was lowered and occasionally reversed. In lobar pneumonia the proteins were more markedly affected than in other acute infections. During the crisis, reversal of the albumin-globulin ratio was the rule. On the whole, the picture was often practically the same as that found in acute and chronic glomerulonephritis and lipoid nephrosis.

Cases of cardiac decompensation with edema showed a moderate reduction of total protein and albumin, a variable increase in globulin and a lowered, and at times a reversed, albumin-globulin ratio.

The cases of carcinoma, with a single exception, showed about the same changes.

Cases of starvation with edema presented low total protein and albumin, increased globulin, and a lowered, and at times a reversed, albumin-globulin ratio. In one case, the albumin fell to 0.66 per cent. Several cases of starvation without edema showed essentially the same changes as those with edema.

One of the two cases of pyelonephritis studied showed a moderate reduction of albumin and total protein, a slight rise in globulin, and a lowered albumin-globulin ratio. One case of nephrolithiasis presented much the same picture. In the other case of pyelonephritis, the serum proteins were within normal limits. Similar observations are to be found in the literature.

Normal protein values were found in the one case of lymphatic leukemia that was studied, while moderately reduced albumin and total protein values were found in an advanced case of Hodgkin's disease. The albumin-globulin ratio was also lowered.

A single case of acute atrophy of the liver (confirmed at autopsy) displayed lowered albumin and total protein, marked increase in globulin and a reversal of the albumin-globulin ratio.

A case of multiple myeloma showed markedly increased total protein and globulin, with normal or moderately reduced albumin. The albumin-globulin ratio was consistently reversed.

From my own observations, as well as from data recorded in the literature, it would seem that a decrease of the total serum protein and albumin, accompanied by an increase in globulin and a lowered or reversed albumin-globulin ratio, is *not distinctive of lipoid nephrosis* or of acute, subacute or chronic glomerulonephritis. The occurrence of similar, and at times nearly identical, changes in a group of diseases so unrelated as acute infections, lobar pneumonia, cardiac decompensation, carcinoma, acute atrophy of the liver and dietary deficiency furnishes support for this observation. Because of the marked

similarity in the serum protein pictures in lobar pneumonia and acute nephritis, Bookman, Findlay, and Tileston and Comfort stated that the impairment of renal function which they found in pneumonia was due to acute nephritis. Normal renal function in pneumonia was found, however, by Reimann, Longcope and Peters, Lewis and Frothingham.

On the whole, it seems logical to conclude that a reduced or reversed albumin-globulin ratio is not pathognomonic for any one disease. Any infection or intoxication (Hurwitz and Whipple), as well as the diseases enumerated, and even the injection of an irritant (von Faikas) can cause it. Corbin suggested that the albumin-globulin ratio is merely an index of the amount of tissue destruction, while Hurwitz and Whipple attributed the lowering and reversal to a metabolic disorder.

The Cause of the Changes in the Serum Proteins—There is much uncertainty regarding the cause of the protein alterations in disease. In some of the nephropathies, e. g., lipid nephrosis, the low total serum protein and albumin may be due to loss of albumin in the urine (Epstein and Vandorfy). Kollert, Linder, Lundsgaard, and van Slyke, Fahr and Swanson, Govaerts and Geill granted that while loss of albumin in the urine may be a factor, it fails to explain the entire picture. Kollert pointed out that lobar pneumonia without albuminuria frequently shows practically the same changes in serum proteins as does nephrosis. The analyses on serum proteins in renal disease and in lobar pneumonia reported in this paper are entirely in accord with the observations of Kollert. In none of the cases of lobar pneumonia listed in table 12 was more than a trace of albumin shown, yet the total protein was low and the albumin-globulin ratio was reversed. Several of the cases of acute infection reported, those of carcinoma, those of cardiac decompensation with edema and those of dietary deficiency showed similar changes. Fahr and Swanson found the same conditions in a case of hyperpiesia without albuminuria. Govaerts found an albumin-globulin ratio of 0.36 in a cardiac case with edema but no albuminuria.

Conversely, in preeclamptic toxemia with persistent heavy albuminuria, there was a normal or nearly normal serum protein. A moderate amount of albuminuria in the case of hypertensive kidney disease caused no alteration in the serum proteins.

The simple loss of albumin in the urine does not explain the increase in serum globulin.

Dilution of the serum (hydremla) has also been suggested as a cause for the lowered total protein and albumin in some forms of renal disease (von Jaksch, Reisz, Rowe, Erben, Askanazy, Strauss, Veil). The more recent work, however, of Schwartz and Kohn, of Linder, Lundsgaard, van Slyke and Stillman, and of Brown and Rown-

tree shows a normal and at times a decreased blood volume in nephritis and nephrosis. The low protein therefore represents a true loss.

Fahr and Swanson reached practically the same conclusion, adding that even if there were a dilution it would fail to explain the increase in globulin.

A disturbance or alteration in protein production was suggested by Linde, Lundsgaard and van Slyke.

The lowering of the serum protein values in lobar pneumonia and in acute infections is due to a thinning of the blood, according to von Jaksch, Askanazy and Rowe. It is difficult, however, to explain the increased globulin values on this basis, unless it is assumed that there is an increased globulin production under these conditions. Albuminuria fails to explain the low serum albumin, for in the majority of the cases the urines were protein-free. Occasionally one would show a faint trace. Stalling and Winands found the same in their cases. In lobar pneumonia there is, of course, some loss of protein in the alveolar exudate. It seems more probable that the protein alterations are due to the infection and intoxication (Huitwitz and Whipple) or to the degree of tissue destruction (Coibin).

According to von Jaksch, Askanazy, Strauss, Veil and Brown and Rowntree, there is an increased blood volume in cardiac decompensation with edema. This thinning of the blood might therefore explain the low albumin and total protein found in this condition, but not the increased globulin. Chiray stated that the blood volume is at times decreased in cardiac cases with edema.

There is an increase in blood volume in carcinoma (Galehi, von Jaksch, Loeper and Tonnet), pregnancy with edema (Zangemeister, Dienst) and malnutrition with edema (Jansen). In malnutrition, the lack of protein in the diet no doubt plays a large part in the causation of low serum protein.

The outstanding difficulty in attempting to explain the serum protein alterations as due to a dilution or thinning of the serum is that, while this no doubt accounts for the lower total protein and albumin, it fails to explain the increased globulin.

The Rôle of Plasma and Tissue Proteins in the Causation of Edema—A direct relationship between low serum proteins and visible edema has been suggested by Reisz, Rowe, Facio, Csartary, Rabinowitch and Childs, Bookmann, Stalling and Winands, Mason and Epstein. The serum proteins have a small but significant osmotic pressure (Stalling, Verney, Cope), and a decrease in their concentration might lower their osmotic pressure to a point at which it would be a factor in the production of edema (Frisch, Mendel and Peters, Epstein, Fishbeig, Govaerts).

In the original work reported in this paper, no constant relationship could be established between low serum proteins and edema. Low serum proteins were frequently found with edema, but the association was by no means constant. The same conclusion was reached by Linder, Lundsgaard and van Slyke, Fahr and Swanson, Bannick and Keith, von Faikas, Schwartz and Kohn, and Cope. Fahr and Swanson, for example, had a case of acute nephritis with marked edema that showed a total serum protein of 8.4 per cent, albumin of 5.2 per cent and globulin of 3.2 per cent. Linder, Lundsgaard and van Slyke at times found no edema when the total serum protein had fallen to 4.5 per cent. They pointed out that although the colloid osmotic pressure is often low in nephritis and nephrosis, no constant parallelism can be demonstrated between this lowered osmotic pressure and edema. Cope added that there is no relation between colloid osmotic pressure and edema of cardiac origin. J. Munk, von Jaksch and Nonnenbruch found high serum protein values in cases with severe edema.

This lack of correlation between low serum protein and edema, which was first pointed out in the summary of the analyses on renal diseases, becomes even more apparent as the serum protein values found in other diseases are considered. In lobar pneumonia, for example, the total protein fell just as low as in the average case of glomerulonephritis and lipid nephrosis, yet no edema developed. Conversely, the same low total protein values were accompanied by edema in all the cases of cardiac decompensation. In several of the cases of pre-eclamptic toxemia, moderate edema was found in the presence of a nearly normal total protein. Malnutrition and starvation gave practically the same serum protein picture regardless of edema.

It was found, however, as previously suggested by Linder, Lundsgaard and van Slyke, that total protein values of 4 per cent and less were constantly associated with edema regardless of the type of renal disease.

In the analysis reported here, low serum protein was generally accompanied by low albumin and a lowered or reversed albumin-globulin ratio. This relationship, however, was not constant. In one case of chronic glomerulonephritis (no. 23) there was a total serum protein of 3.94 per cent, but the albumin-globulin ratio was not reversed. Conversely, a lowered and at times reversed albumin-globulin ratio was occasionally associated with normal total protein.

Low serum albumin is the main cause of edema, according to Barker and Kirk and Dienst. Govaerts, von Faikas and Cope concluded that the "specific colloid osmotic pressure" has a direct relation to the magnitude of the albumin-globulin ratio. A low albumin-globulin ratio

therefore indicates a low "specific colloid osmotic pressure," and thus causes edema (Facio, Rusznyák, Barát and Kurthy)

The original observations reported here did not show a constant relationship between edema and low albumin-globulin ratio. In the cases of renal disease studied, low and reversed albumin-globulin ratios were often not associated with edema, while nearly normal ratios frequently accompanied marked edema. In lobar pneumonia, a few severe acute infections and acute atrophy of the liver, in which the albumin-globulin ratio was strikingly reversed, no edema could be made out. In preeclamptic toxemia, malnutrition, and cardiac decompensation, edema occurred irrespective of the magnitude of the albumin-globulin ratio.

Albumin values of 0.8 per cent and less, as pointed out by Barker and Kirk, were, however, always accompanied by edema. Kohman, Denton and Kohman, Mavei and Frisch, Mendel and Peters, in their experimental work, found that nutritional edema was directly dependent on low protein and high water intake. The same has repeatedly been observed with edema occurring during famine and war. Both factors must be operating. In the cases of malnutrition reported in this paper, no edema developed when the patient took neither food nor water. Frisch, Mendel and Peters pointed out that while the serum protein is lowered as much as 40 per cent and the colloidal osmotic pressure necessarily falls, these phenomena are not wholly responsible for the edema. Rather the low serum protein determines a tendency toward water retention, which is probably influenced by other factors.

Whether edema of the tissues is accompanied by "edema of the blood" (hydiemia) is a disputed point. In nephritis with edema there is a thinning of the blood (Bright, von Jaksch, Eiben, Reisz, Askanazy, Rowe, Strauss, Veil). This is denied by Linde, Lundsgaard, van Slyke and Stillman, by Brown and Rowntree and by Schwartz and Kohn. The same disagreement is found as regards cardiac decompensation with edema (Chiray, von Jaksch, Askanazy, Strauss, Veil, Brown and Rowntree). On the other hand, hydiemia has been described as occurring in febrile diseases (von Jaksch, Askanazy, Rowe) and in carcinoma (Galehr, von Jaksch, Loeper and Tonnet). No edema is present in these conditions.

From the available evidence, therefore, it would appear that no constant relationship exists between tissue edema and hydremia.

It has been suggested by Maxwell, by Achard, Ribot and Leblanc, by Dyke and by Stepp that there is a direct relationship between the amount of blood cholesterol and edema in acute nephritis. Maxwell added that no such correlation exists in chronic parenchymatous nephritis. Strauss thought that edema in nephritis may be due to an

altered cholesterol-lecithin ratio Hahn and Wolff, Beumer, and Schwartz and Kohn were unable to find any relationship between blood lipoids and edema Von Faikas showed that the addition of lecithin and cholesterol reduces the specific colloid osmotic pressure of the serum A reciprocal relationship between the serum proteins and fats was found by Fishbeig As the colloid osmotic pressure fell, secondary to the loss of serum proteins, the lipid content of the serum rose in an attempt to build up the lowered osmotic pressure Kollert attributed much of the edema of nephritis to an increase of hydrophil fibrin in both the blood and the tissues

In considering edema from the standpoint of protein, it is first of all necessary to recognize both blood and tissue proteins as constituting a part of a highly sensitive hydrophil colloid system Components of such a system display a small but definite osmotic pressure and an equally important imbibition or swelling pressure Their physical structure may be altered and their action modified by changes in hydrogen ion concentration, by the anions and cations enumerated in the Hofmeister series and by adsorption of substances on their surfaces All these can influence the degree of hydration of the colloid Water bound by the colloids can again be lost (syneiosis) (Gortner)

The colloids of the blood are separated from the colloids of the tissue spaces by the capillary wall, which possesses many properties common to a dialyzing membrane The colloids of the tissue spaces are in turn separated from those in the cell by the cell wall, which may act as an osmotic membrane (Schade and Menschel)

The membranes themselves are probably made up of hydrophil colloids and would accordingly be sensitive to all the factors just enumerated

Under normal conditions, a Donnan equilibrium exists around the capillary or dialyzing membrane This results in an unequal distribution of electrolytes on the two sides of the membrane and consequently an osmotic system is established By this osmotic action, water is pulled from the tissues into the blood (Rusznayák, Barát and Kurthy) In this the serum colloids no doubt play a small but definite rôle

Under abnormal conditions resulting in the production of edema, many changes take place in the colloids of the blood, membranes and tissues The imbibition capacity of the serum colloids may be in some way modified or increased (Thomas and Andrews) or their degree of dispersion altered, owing to the presence of some foreign substance in the blood

The capillary wall, owing to its component hydrophil colloids, may have its permeability altered by this same substance (Cohnheim, Reisz, Georgopulos, Schlayer, Volhard) Such a possibility was denied by

Kolleit and by Engel and Olszag. Full evidence in favor of an increased permeability of the capillary membrane is furnished by the fact that the edema fluid in all cases contains an excess of protein (both albumin and globulin).

As a result of this altered permeability, the entire osmotic balance around the capillary wall is upset.

The same foreign substance can well alter the imbibition capacity of the tissue colloids, causing them to take up more water (Thomas and Andrews). The entrance of the serum proteins into the tissue fluids may likewise influence imbibition and thus play a part in edema (Eppinger, Schade and Menschel, Kisch).

The water thus imbibed by the tissue colloids is held ("bound") in a different way from that in which it is held under normal conditions (Steggerda). There is now a much greater tendency for the colloid to hold tightly to the imbibed water.

Finally, owing probably to some change in the surrounding media or to some alteration in the tissue colloid itself, the bound water is released and then lies free in the tissue spaces (syneresis).

A few independent experiments were undertaken along lines similar to those followed by Steggerda in his work on bound water. Muscles were taken from edematous frogs, thin unstained frozen sections made, and several hundred of the individual muscle bundles measured. These were compared with an equal number of measurements made on muscles of normal frogs. Without exception, the muscle bundles of the edematous frogs showed a greater diameter than those of the normal frogs. This difference ranged from 22 to 30 per cent. It was further observed that swollen frogs that showed large amounts of free water beneath the skin and between the muscles showed less swelling of muscle bundles than did those frogs that were distinctly swollen, but that had little free water beneath the skin or between the muscles.

The cause of edema in these frogs is unknown. The kidneys were studied in all cases, but these showed nothing abnormal.

While it is admitted that it is unsafe to attempt to interpret human edema in terms of edema observed in a frog, it is nevertheless plausible to assume, from the known physical and chemical properties of colloids as well as from experiments in blood and tissue colloids on human material (especially the work of Schade and Menschel), that in edematous states, some of the excess water is held ("bound") by the tissue colloids, while the remainder lies free in the tissue spaces.

The foregoing discussion of edema gives merely a picture of colloid changes that may possibly be taking place under certain abnormal conditions. The causes, or inaugurating factors, of such changes are not known. No doubt they are many and varied.

From the original work and observations recorded here, as well as from some data gathered from the literature, it seems fair to assume that alterations in serum proteins do not in themselves adequately explain edema of any kind. They reflect, rather than inaugurate, the changes giving rise to edema.

It might also be suggested that nothing is to be gained from the separation of serum protein into its albumin and globulin fractions. This separation is entirely arbitrary and artificial and does not represent the protein as it existed in the body. Perhaps there is only a single large protein aggregate in the serum, which, because of its inherent colloidal properties, may be so altered in disease that it responds differently when subjected to the action of different salts in the test tube.

CONCLUSIONS

In all forms of renal disease considered here, except hypertensive kidney, in which normal serum protein values were found to be the rule, the total protein and albumin were lowered, the globulin was increased, and the albumin-globulin ratio was lowered and frequently reversed. Values approaching the normal were infrequently found. There were no protein changes pathognomonic for any one type of renal disease.

Lobar pneumonia gave a picture very much like that found in renal disease, in that there was a marked reduction in albumin and total protein, a distinct increase in globulin and a persistent reversal of the albumin-globulin ratio. This was true only during the crisis. Other acute infections showed the same, but less marked changes.

In cardiac decompensation with edema, there was a moderate reduction in albumin and total protein, with a moderate increase in globulin and a lowered, and at times reversed, albumin-globulin ratio.

In advanced carcinoma, the albumin was constantly reduced, while the globulin was normal or slightly increased. With a single exception, the total protein was lowered. The albumin-globulin ratio was slightly reduced, on one occasion it was reversed.

In malnutrition with edema, the albumin and total protein were moderately reduced, while the albumin-globulin ratio was moderately lowered. Starvation without edema gave the same picture. In one case with massive edema, unusually low albumin and total protein values with increased globulin and a striking reversal of the albumin-globulin ratio, were found.

Practically normal values were found in a case of lymphatic leukemia, while a case of advanced Hodgkin's disease showed normal globulin, but a moderate lowering of albumin and total protein.

Unusually high values for globulin and total protein with normal or moderately reduced values for albumin, were found in a number of analyses in a case of multiple myeloma

Acute atrophy of the liver, kidney stone and one case of pyelonephritis showed a moderate lowering of albumin and total protein with some elevation in globulin. The albumin-globulin ratio was reversed in acute atrophy of the liver. Normal protein values were found in a second case of pyelonephritis

Normal protein values were the rule in preeclamptic toxemia

Analysis of a limited number of anasaricous, ascitic and pleural fluids showed the presence of both albumin and globulin. The protein content varied with the type of disease and possibly also with the location of the fluid

A comparison of the results secured by the refractometer and by the micro-Kjeldahl method showed that they agree fairly well except as concerns lipemic milky serums. Here the total protein and at times the globulin values given by the refractometer are much too high

Marked lowering and reversal of the albumin-globulin ratio was not pathognomonic for any one disease or group of diseases. It appeared to be more directly related to the degree of infection and intoxication or to that of tissue destruction

No constant correlation could be established between edema and low serum protein, or between edema and reversal of the albumin-globulin ratio. Neither was there any constant relationship between low serum protein and reversal of the albumin-globulin ratio

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STUDIES OF CALCIUM AND PHOSPHORUS METABOLISM

IX DEPOSITION OF CALCIUM IN BONE IN HEALING SCORBUTUS*

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In studying calcium metabolism, and particularly the storage of calcium within bone, Bauer, Aub and Albright¹ pointed out that the spicules along the medullary canal and in the cancellous portion of the ends of long bones were markedly resorbed in animals fed a diet low in calcium. They demonstrated that after the receipt of a diet high in calcium new bone was laid down only in the trabeculae. This was partly determined by the use of alizarin red, which stains only newly formed bone deep red. In order to determine the site of repair in general metabolic disturbances which affect bone, the dye has been again used to mark newly deposited calcium. In view of the slow progress of the metabolism of bone it was expedient to study a process which would produce a rapid change in bone, so that confusion with slow alterations in normal deposit of calcium might be avoided. Such rapid variations occurred in the work of Wolbach and Howe,² who showed that guinea-pigs became scorbutic in about two weeks when they were fed diets deficient in vitamin C. We have used their work as a means of studying the site of loss of calcium from the bones from other than physiologic causes.

METHODS

Young adult guinea-pigs, each weighing about 500 Gm., were housed in cages containing a very small amount of sawdust. They were fed the scorbutus-producing diet described by Wolbach and Howe, with shreds of filter paper for roughage. Usually during the third week the animals began to show a disturbance of the joints by their quietness and stiff gait. During the fourth week they ate poorly, and shortly thereafter died, unless given orange juice.

Sodium alizarin sulphonate was used in a saturated solution (nearly 2 per cent) in physiologic solution of sodium chloride. The injection of 0.5 cc. of this intra-

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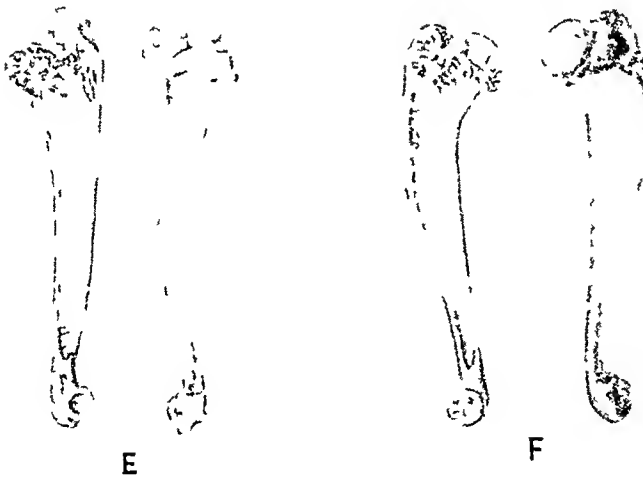
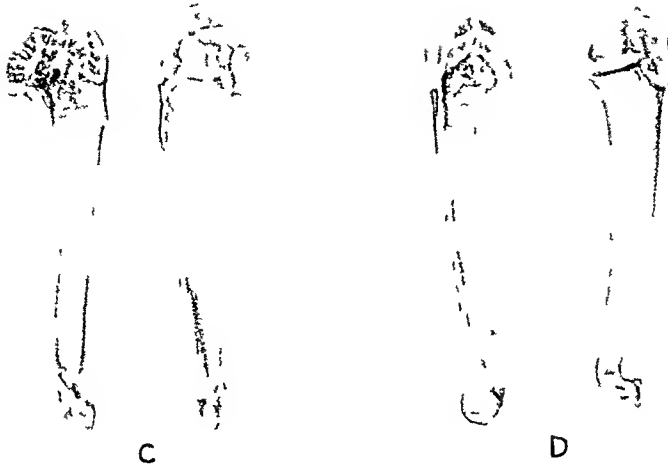
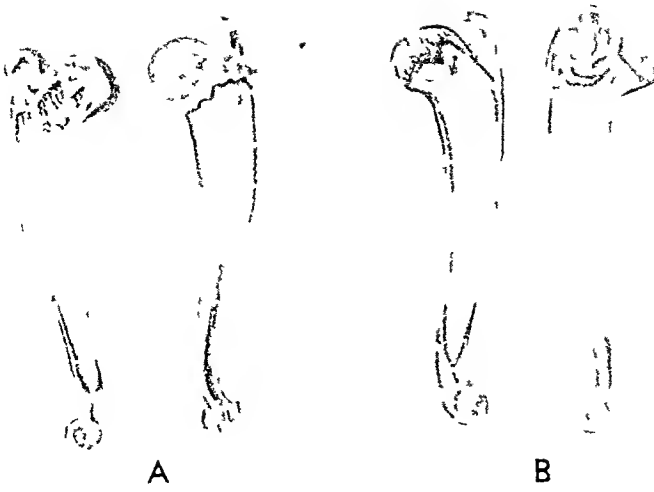
* From the Medical Clinic of the Massachusetts General Hospital.

* Aided financially in part by the Lead Fund of the Harvard School of Public Health.

- Miss Frances M. Angier prepared the diet.

1. Bauer, Aub, and Albright. A Study of the Bone Trabeculae as a Readily Available Reserve Supply of Calcium, *J. Exper. Med.* **49**: 145, 1929.

2. Wolbach and Howe. Intercellular Substances in Experimental Scorbutus, *Arch. Path.* **1**: 1, 1926.



The influence of orange juice on the deposit of calcium in guinea-pigs maintained on a diet otherwise deficient in Vitamin C

A, the humerus from a guinea-pig that received both orange juice and alizarin red from the twenty-first to the thirty-fourth day of a scorbutic diet

B and *C*, the humeri of a guinea-pig that received both orange juice and alizarin red from the thirtieth to the forty-first day of a scorbutic diet

D, the humerus of a guinea-pig that received both orange juice and alizarin red from the thirtieth to the forty-fourth day of a scorbutic diet

E, the humerus of a control guinea-pig that died on the thirtieth day of a scorbutic diet without orange juice or alizarin red

F, the humerus of a control guinea-pig that received orange juice and alizarin red from the start of the scorbutic diet, and was killed after seven weeks

peritoneally usually proves toxic and may indeed kill the guinea-pig. Most of our injections therefore were given intramuscularly in the gluteal region twice a week.

The humerus was selected as the bone for investigation in this series. It was split by means of the circular mechanical dental saw recommended by Howe, and the two halves of the bone were digested in a mixture of pancreatic trypsin and bile or in duodenal contents, buffered at pH 8. The final cleaned specimen was preserved in an alkaline formaldehyde (10 per cent) solution.

Unless the organic matter is completely removed, there remains behind a dirty-brown discoloration of the bone, which may obscure the color of the alizarin, occasionally hemoglobin persisting in a freshly split bone may simulate this color, especially when fresh periosteal hemorrhages have been present. For this reason bones of scorbutic animals that had received no dye were used to control the technic of digestion. These bones were nearly ivory white. It was at first intended to follow the same experimental procedure used by Bauer, Aub and Albright, in which a foreleg was amputated as a control of the changes in the contralateral bone. The scorbutic animals ate so poorly after operation, however, that this method of procedure was finally abandoned, and control animals were relied on to check the experiment.

The effect of the injection of alizarin blue black B also was tried on growing rats and kittens, and on the teeth of adult rodents (rats and guinea-pigs). Injections of the blue dye were made at weekly intervals for from six to eight weeks, and the animals, watched for many months, were killed at occasional intervals. Although control animals that had received injections of alizarin red showed reddening of the teeth or bone, there was no evidence of deposition of the blue color in the teeth or in growing bone, the retroperitoneal lymph nodes and lymphatic channels, however, were filled therewith.

As the actual amount of new bone laid down during the few weeks of the experiments on guinea-pigs was much smaller than in the case of a fracture-callus³ or even of new spicules laid down under prolonged feeding of diets of high calcium content, care had to be taken not to remove mechanically or chemically a thin, bony external film containing alizarin. Some of the tissue was osteoid in consistency, and as it digested out left small fragments of better calcified tissue unsupported or only poorly adherent. The color change, too, was not so striking as in the experiments mentioned earlier, in which more calcium was deposited.

COMMENT ON THE RESULTS

The accompanying figure indicates the sites of the deposition of alizarin in the bones of animals used in typical experiments. The distribution of dyestuff in the humerus followed the classic description of scorbutic lesions. The epiphyseal line was particularly well marked, this was seen both externally and within the split bone. The cancellous tissue of the epiphysis and diaphysis was stained, and pink spicules extended a short way into the medullary cavity. Externally, the shaft near the head distal to the epiphyseal line was usually stained for a variable, but considerable, distance, and frequently a large patch of red was found along the distal portion of the body of the bone, suggesting this as the site of a previous subperiosteal hemorrhage. There was

³ Brooks, Barney. Studies in Regeneration and Growth of Bone, *Ann Surg* 65 704, 1917, Studies in Bone Regeneration, *Ann Surg* 66 625, 1917.

greater involvement of the trabecular portions of the bone as contrasted with the shaft

The bones of control animals receiving no orange juice or receiving orange juice from the commencement of the diet showed no deposition of alizarin. Some control animals receiving alizarin during the production of scurvy showed at death slight reddening of the exterior of the bone, but no dye in the trabeculae. In one successful operative experiment, in which a fore limb was amputated after twenty-eight days of the scorbutic diet (two weeks after abortion), no appreciable amount of dye was detected, although injections of alizarin had been proceeding for three weeks. The contralateral leg, after five weeks' feeding of orange juice, showed reddening of both spicules and the external shaft. These control experiments indicated little or no deposition of calcium during acute experimental scorbutus.

The specimens indicated macroscopically the extent to which the healing of acute scorbutus may precipitate new formation of bone. The experiments of Wolbach and Howe indicated that the healing process in scorbutus involves the setting of a material already present. It was by no means certain, therefore, that alizarin would be deposited in such a matrix when it solidified with the deposition of calcium salts. Our observations show that newly deposited lime salts produced by the healing of a metabolic disease may be marked by alizarin red just as is newly formed bone in other processes not connected with vitamin deficiency. Gyorgy⁴ has just published roentgenologic evidence following overdosing with viosterol, corresponding to these results.

It is evident that the supply of vitamin may rapidly affect the deposition of calcium within the trabeculae, and that the reserve store of calcium is influenced by the vitamin, as well as by the calcium of the diet and the parathyroid hormone. It is probable, however, that the mechanism is quite different, for with the deficiency in vitamin it is the underlying cellular structure⁵ that is primarily at fault.

SUMMARY

Calcium fails to be deposited in bone when the diet, though adequate in calcium, is deficient in vitamin C. The subsequent addition of vitamin C to such a diet allows calcium to be rapidly deposited.

This deposit is largely at the epiphyseal ends of the bone and in the trabeculae. In other words, not only growth, but also the stores of the reserve supply of calcium are involved by the pathologic changes in the bone cells.

⁴ Gyorgy, P. Die besondere Stellung der subepiphysaren Knochenschicht im Kalkstoffwechsel als eines leicht mobilisierbaren Kalkspeichers, *Klin. Wchnschr.* 9 102, 1930.

⁵ Wolbach and Howe (footnote 2).

PARADOXICAL EMBOLISM

L R FRENCH

BALTIMORE

The chance of seeing a thrombus pass through the foramen ovale is so rare that the following case is worthy of note

A woman, aged 36, died twenty-nine days after hysteromyomectomy and after having shown various clinical evidences of embolic occlusion of branches of the pulmonary artery. At autopsy, an old embolus was found completely obstructing the branch of the right pulmonary artery leading to the lower lobe and partially blocking the middle and upper branches. The time of its lodgment was apparently indicated by an abrupt rise in temperature and pulse rate, with a pain in the lower part of the right side of the chest on the sixth day after operation. A partially organized embolus filled the entire left pulmonary artery, and its arrival was marked by a sudden rise in the pulse rate on the twenty-fourth day. A third fresh embolus occluded the remaining upper branches of the right pulmonary artery and had lodged there at the time of the last acute clinical symptoms fifteen minutes before death.

The heart showed a long thrombus caught half way through the foramen ovale, so that part hung in the right auricle and the rest in the left (figs 1 and 2). From its form, it had evidently been molded in a vein, but so many large emboli had already been dislodged that it is impossible to be sure of its point of origin. The great obstruction of the pulmonary circulation, which has been observed in about half of the cases of this sort already reported, must have increased the blood pressure in the right side of the heart and caused its dilatation, decreasing the pressure in the left auricle, a condition thought to favor paradoxical embolism. This must also have favored the twisting and turning of the embolus, which finally penetrated the foramen ovale, while still in the right auricle, for it was the distal end of the mold of the vein that had passed into the left auricle.

The embolus was 16 cm long and in the form of a tapering cylinder. The part which still hung in the right auricle was 1 cm thick and grayish. About 1 cm of it remained in the right auricle, its end dividing into two short branches—broken stumps evidently formerly continuous with another portion that may have been dislodged previously. In the left auricle, the rest of the embolus hung down 5 cm, passing through the mitral ring to a point 0.5 cm below the margin of the leaflets. There it folded back on itself for nearly 4 cm, terminating in a second U-shaped fold in the left auricle. This terminal part measured only 4 mm in thickness and was dark red.

No special symptoms could be expected from this plugging of the foramen ovale, and it is evident that there was no time for the embolus to be broken and thrown in fragments into the systemic arterial circulation. No evidence of embolism of arteries in other organs was found.

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From the Department of Pathology of Johns Hopkins University



Fig 1—Right auricle Remainder of embolus projecting from the foramen ovale

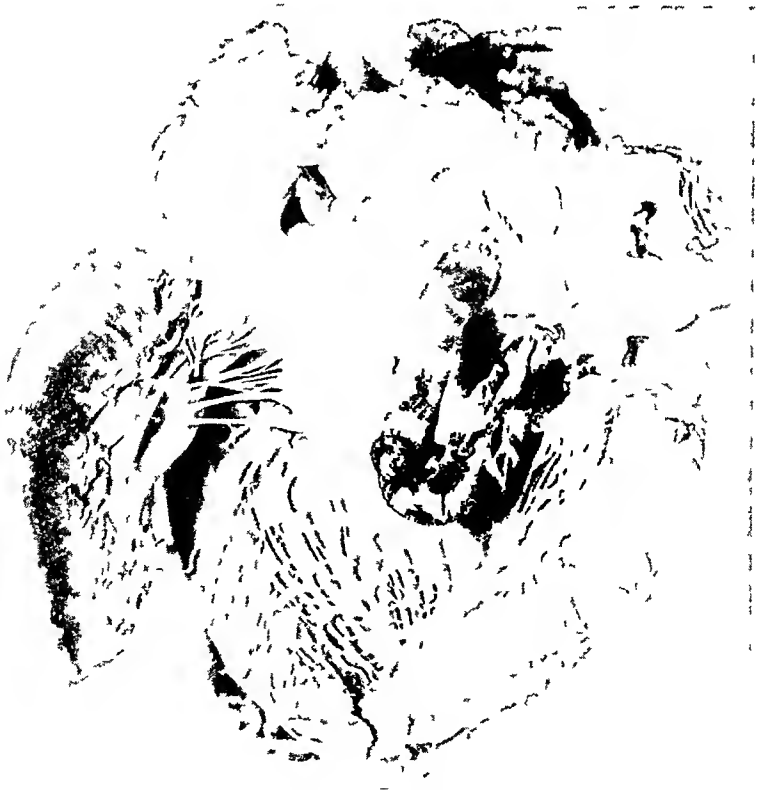


Fig 2—Left side of the heart Embolus hanging from foramen ovale and down through the mitral orifice

PRIMARY NEOPLASMS OF THE PLEURA

A REPORT OF FIVE CASES ~

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Although primary pleural neoplasms are classed among the rarer types of tumors, their importance has been recognized in a rather extensive literature. Their histogenesis and their classification are still subjects of controversy. A study of the entire group of pleural tumors permits a classification which appears to be of value, not only theoretically, but also from a practical standpoint, for the recent advancement in thoracic surgery has made the successful removal of some of these growths possible.

Macroscopically the tumors may be sharply divided into two main groups. The first consists of those primarily localized in one part of the pleura. The second consists of those of a diffuse nature, involving the entire pleura and usually ensheathing the lung in tumor tissue. The latter group is mainly of academic interest, it forms the subject of the second part of this paper.

LOCALIZED TUMORS OF THE PLEURA

Localized tumors of the pleura may involve the parietal or the visceral layer. They comprise many histologic types and benign and malignant forms. The entire group is possessed of a common characteristic: they originate from the tissues beneath the superficial lining cells, in contradistinction to the diffuse form of pleural tumors, which probably arise from the surface lining.

Tumors arising from beneath the parietal pleura of the wall of the chest vary greatly in their histologic structure because of the number of different structures that are present in this region in addition to the subserous areolar tissue. The fascia of the intercostal muscles, the nerve sheaths and the subpleural fat may also be the origin of a localized neoplasm. Malignant connective tissue tumors in this location have been described by Blumenau,¹ Leube,² Israel-Rosenthal (second case),³

* Submitted for publication, Sept. 19, 1930.

~ From the Laboratories of Mount Sinai Hospital.

1 Blumenau, M. B. Primäres Sarkom der Pleura, *Deutsche med. Wchnschr.* 22: 570, 1896.

2 Leube, W. Spezielle Diagnose der inneren Krankheiten, Leipzig, F. C. W. Vogel, 1891, vol. 1, p. 166.

3 Israel-Rosenthal. Beitrag zur Klinik der primären Pleura Sarkome, *Nord med. Ark.*, 1900, vol. 7, cited in *Virchows Jahresbericht* 352: 266, 1900.

Kaufmann⁴ and Hofmohl⁵ They were all large In Hofmohl's case, the neoplasm weighed 7 pounds (3.2 Kg) The tumors were described as round cell sarcoma, spindle cell sarcoma and angiosarcoma They invaded the wall of the chest and metastasized to the visceral pleura, to the mediastinal lymph nodes and occasionally to the abdominal organs Pallasse and Roubier (case 1⁶) reported a lipomyxosarcoma originating from the subpleural fat over the diaphragm, and Barbier and Molland⁷ described a malignant fatty tumor arising from beneath the mediastinal pleura Jacobaeus and Key⁸ and Sabrazes and Muratet⁹ reported similar tumors originating from the fat tissue beneath the wall of the chest Benign connective tissue tumors in this location were described by Jacobaeus and Key (cases 2, 3 and 4)⁸ Neurosarcomas originating from the intercostal nerves were first described by Grawitz,¹⁰ who mentioned five cases from his experience In one of these cases metastases developed Banse,¹¹ Kobilinsky¹² and Schmidt (second case)¹³ described similar cases Stewart and Adam¹⁴ described a sarcoma beneath the costal pleura in which the intercostohumeral nerve was embedded The tumor was encapsulated, but had eroded the cartilages of the ribs

On the other hand, the tumors reported arising from the subserous layers of the visceral pleura were generally not of an invasive character A number of small growths, fibromas, leiomyomas, lipomas and chon-

4 Kaufmann, E Spezielle pathologische Anatomie, Berlin, W de Gruyter & Company, 1922, vol 1, p 385

5 Hofmohl Endothelsarkom der rechten Pleura, Arch f Kinderh **7** 81 1885

6 Pallasse, E, and Roubier, C Les tumeurs primitives de la pleure, Ann de med **3** 243, 1916

7 Barbier, J, and Molland, H Un cas de tumeur maligne mediastins pleurale avec l'aspect histologique de lipo-sarcome, Lyon med **138** 623, 1926

8 Jacobaeus, H C, and Key, E Some Experiences with Intrathoracic Tumors, Their Diagnosis and Their Operative Treatment, Acta chir Scandinav **53** 573, 1920-1921

9 Sabrazes, J, and Muratet, L Myxome lipomateux, intra-thoracique Arch de méd exper et d'anat path **21** 580, 1909

10 Grawitz, P Demonstration einer neuen Gruppe intrathorakaler Tumoren, Deutsche med Wchnschr **34** 1123, 1908

11 Banse Ueber intrathoracische Fibrome, Neurome und Fibrosarkome, Inaug Diss, Greifswald, 1908

12 Kobilinsky Ueber primare Sarkome in der Lunge, Inaug Diss, Greifswald, 1904

13 Schmidt, W Ueber Fibrome der Lungenpleura, Inaug Diss, Greifswald, 1903

14 Stewart, J, and Adam, J G Case of Primary Angiosarcoma of Upper Portion of Left Pleura, Montreal M J **22** 1909, 1893-1894

diomas in this location, found accidentally at postmortem examination, have been described in the literature. They will not be discussed in this paper.

By far the most interesting and important group of localized sub-pleural connective tissue neoplasms consists of the so-called giant sarcomas of the visceral pleura. Their pathologic interest lies in the fact that the tumors described in the literature did not metastasize or infiltrate, in spite of the microscopic picture of sarcoma. Clinically, they are of importance because, if diagnosed early enough, they may be removed, and because, if neglected, they cause death from disturbances in circulation due to the extreme proportions to which they grow.

Sixteen cases corresponding to this type have been described in the literature by Dorendorf,¹⁵ Schneider,¹⁶ Mehrdorf,¹⁷ Braun,¹⁸ Kaufmann,⁴ Nevinney,¹⁹ Ricard,²⁰ Quincke and Garre,²¹ Henke,²² Israel-Rosenthal (case 1),⁷ Kidd and Habershon,²³ Schmidt (case 1),¹³ Kahler and Eppinger,²⁴ Podack (case 3),²⁵ Sala,²⁶ and Pallasse and Roubier (cases 2 and 3).⁶

The tumors reported evidently grew very slowly and were present for many years before they gave rise to symptoms. By this time they were very large. The larger ones, in each case, practically filled one side of the thoracic cavity displacing the heart and compressing the

15 Dorendorf, H. Demonstration einer grossen Pleuratumors, Deutsche med Wchnschr **40** 225, 1914

16 Schneider, J. Ein anatomisch und klinisch umschriebener Typus des Pleurasarkoms. Virchows Arch f path Anat **252** 706, 1924

17 Mehrdorf, R. Fibrosarcoma myxomatoides pleurae permagnum, Beitrag zur Kenntnis der primären Pleuratumoren, Virchows Arch f path Anat **193** 92, 1908

18 Braun, H. Demonstration eines Tumors der Pleura, Verhandl d deutsch Gesellsch **37** 162, 1908

19 Nevinney, H. Beitrag zur Casuistik der "Expansiv wachsenden Pleuramesenchymosarkome," Mitt a d Grenzgeb d Med u Chir **40** 277, 1927-1928

20 Ricard, M. Volumineux sarcome intra-thoracique d'origine pleurale, Bull et mem Soc de chir de Paris **34** 804, 1908

21 Quincke and Garre. Lungenchirurgie, ed 2, Jena, Gustav Fischer, 1912, p 193

22 Henke, F. Mikroskopische Geschwulstdiagnostik, Jena, Gustav Fischer, 1906, p 238

23 Kidd P, and Habershon, S. H. Primary Myxo-Sarcoma of the Pleura, Tr Path Soc London **49** 15, 1898

24 Kahler, O, and Eppinger, H. Ein Fall von intrathoracischem Tumor, Prag med Wchnschr **7** 242, 1882

25 Podack, M. Zur Kenntnis des sogenannten Endothelkrebs der Pleura, Deutsches Arch f klin Med **63** 1, 1899

26 Sala, A. M. Large Fibrosarcoma (?) in the Pleura, Arch Path **9** 950, 1930

lung Death resulted from cardiac failure because of obstruction to the pulmonary circulation. This was evidenced by the enlargement of the right ventricle (Kahlei and Eppinger,²⁴ Podack²⁵ and Nevinney¹⁹) and atherosclerosis of the pulmonary artery (Podack²⁵).

The smaller tumors (Schneider,¹⁶ Garie²¹) were irregular, rounded, lobulated growths, firm in consistency and gray with green and red mottlings due to degeneration and hemorrhage.

The tumors, in each case, were enclosed in a connective tissue capsule which was covered by a smooth membrane continuous with the visceral pleura. The tumors were pedunculated, and they often became secondarily adherent to the diaphragm, the costal pleura, the pericardium or other lobes of the lung. The connections between the tumor and the points of origin, as well as the points of adhesion, were usually small bands. Whereas this made for ease of removal, it often made difficult the determination of the exact point of origin. Thus Dorendorf,¹⁵ Schneider¹⁶ and Pallasse and Roubiet⁶ believed that in their cases the origin was from the pleura over the diaphragm.

The microscopic picture, usually that of a fibrosarcoma, varied somewhat in different cases. The case of Kahlei and Eppinger²⁴ was that of a simple fibroma. Most of the others were described as spindle cell sarcoma with areas less cellular resembling fibroma and areas simulating round cell sarcoma. Kidd and Habershon,²³ Mehidoif¹⁷ and Israel-Rosenthal³ reported myxomatous changes in their cases, and Schneider¹⁶ reported the finding of giant cells. In general the picture was that of fibrosarcoma, growing to large proportions with no evidence of metastasis. In Nevinney's¹⁹ case there was some infiltration of the capsule by spindle cells at the attachment of the tumor to the lung. In spite of this fact, Nevinney believed that it should not be classed with the malignant type of tumors.

In examining the available data, one comes to the conclusion that this view is justified. Whereas it is true that the duration of symptoms before death (as reported in the literature) is relatively short, the size of the tumors, the lack of metastases and the perfect encapsulation speak against malignancy. Evidence of the slowness of growth of what eventually become giant pleural tumors was presented by Wessler and Jaches²⁷ in their roentgen studies. One of us has been able to observe clinically the slow growth of three tumors, which, in all probability, are of a similar nature and which will be the subject of a future communication.

Four cases of giant tumors originating from the subserous layer of the visceral pleura have come under our observation.

²⁷ Wessler, H., and Jaches, L. Clinical Roentgenology of the Chest, Troy, N. Y., The Southworth Company, 1923, p. 296.

REPORT OF CASES²⁸

CASE 1—*History*—F I, a white woman, aged 48, had a slight cough for a number of years, to which, however, she paid little attention. Because of clubbing of her fingers, roentgenograms of the chest were made at the request of her physician, preliminary to the performance of a gynecologic operation. They showed a round shadow in the left side of the chest, measuring about 15 cm. in diameter. A thoracotomy was performed by Dr. Howard Lilienthal, and a tumor was found situated in the anterior portion of the left side of the chest, connected with the lung by broad bands and loosely adherent to the wall of the chest and to the pericardium. It was completely removed.

Macroscopic Examination of Tumor—The specimen received in the laboratory was a round, irregular, nodular tumor, grayish-pink, and measuring 16 by 15 by 7 cm. (fig. 1A). On the mesial surface there projected a large oval node measuring 9 by 5 by 4 cm., which was demarcated from the main tumor by a deep incisure. The entire tumor was surrounded by a smooth, transparent capsule, which contained many blood vessels. There were numerous short fibrous bands on the flat anterior surface. To the upper anterior border there was attached a wedge-shaped piece of flattened lung tissue, the pleura of which was continuous with the capsule of the tumor. The main tumor was very firm, lobulated on section, with whitish streaks, resembling a fibroid tumor. The nodular appendage was softer, and on section it was pink, fleshy and of homogeneous structure, with a few yellow areas of necrosis.

Microscopic Examination—Under low power magnification (fig. 1B), the tumor appeared to consist of rows and nests of cells, which were separated by strands of dense connective tissue. The stroma, which in places was very poor in cells, contained narrow, thin-walled blood vessels, some of which were filled with platelet thrombi. In these regions there were occasional extensive areas of necrosis.

Under higher magnification, the cells appeared uniformly spindle-shaped, with scanty, occasionally branching, cytoplasm and large oval nuclei. The nuclei were poor in chromatin and contained small angular or rounded nucleoli. Mitoses were not seen. Between the cells, which morphologically had the characteristics of fibroblasts, there were many fibers that stained red with the van Gieson stain. These fibers stood in close relationship to the fibroblasts, to which they were in part closely attached and with the protoplasmic processes of which they were in places continuous. The picture of the tumor varied in different portions according to the richness in intercellular fibers. Some parts were more and some less cellular.

Sections from the periphery of the tumor showed it to be surrounded by an acellular fibrous capsule, which was continuous with the pleura over the adjacent lung tissue. The capsule was almost entirely demarcated from the tumor. In a few places, however, it was infiltrated by tumor cells.

The uniformity of the cellular architecture with rows of fibroblasts showing remarkably little variation and the absence of mitoses, together with the macroscopic picture of an expanding growth, would have led to the diagnosis of cellular fibroma. Since, however, there was seen

²⁸ Dr. Howard Lilienthal contributed the clinical data of cases 1 and 2, and gave permission for their inclusion in our report.



Fig 1 (case 1) —*A*, lobular tumor showing lung attached to its superior mesial border, *B*, histologic structure of tumor

microscopically an infiltrative growth of tumor cells in the capsule in a few places, the tumor had to be designated a fibrosarcoma. With further consideration of the clinical condition and the microscopic observations it was felt that a good prognosis could be given, especially since the tumor had been completely removed.

CASE 2—*History*—J. B., a man, 53 years of age, was admitted to Mount Sinai Hospital in November, 1926. He had complained of pain in the left side of the chest for a period of three years. Roentgen examination disclosed a large shadow in the left side of the chest, which was considered to be that of a neoplasm. Operation was performed by Dr. H. Lihenthal on Nov. 23, 1926. The pleural cavity was found to be obliterated by firm adhesions. Beneath the pleura there was a large, hard, whitish-gray, dense, fixed mass. Because of the extensive adhesions this could not be removed, however a portion about the size of a tennis ball was enucleated. Microscopic examination of a section of this material by Dr. F. S. Mandelbaum showed the typical picture of fibrosarcoma. Further tissue removed a short time thereafter was examined at Roosevelt Hospital and fibrosarcoma with a low degree of malignancy was diagnosed. The patient was treated with deep irradiation.

In April, 1930, he was readmitted to Mount Sinai Hospital because of increasing symptoms in the left side of the chest. Again numerous particles of neoplasm were removed by Dr. H. Lihenthal. Roentgen examination of the right side of the chest revealed two sharply circumscribed masses in the right lung.

Microscopic Examination of Tumor—Sections of the tumor removed in November, 1926, showed (fig. 2A) cellular portions composed of spindle cells with a considerable amount of intercellular collagen fibers, and other portions in which the cells were scanty, the fibers forming the bulk of the growth. The tumor cells were uniform in size and shape, and no mitotic figures were found. The diagnosis was fibrosarcoma of a low grade of malignancy.

The specimen received in the laboratory in April, 1930, consisted of several irregular masses of tissue, the aggregate material measuring about 7 by 8 by 5 mm. The portions varied considerably in consistency. Some were soft and rubbery, others were very firm. The former had a yellowish-orange, mottled appearance. On section, they presented a smooth, glistening, homogeneous surface. The central portions showed small areas of necrosis. In places they had a translucent myxomatous appearance. The firm portions of the tumor were grayish white and on section were very dense and fibrous.

Sections of the different portions of the tumor removed at operation showed a varied appearance. The very firm portions were formed by connective tissue unusually poor in cells, together with scattered, thin-walled blood vessels. The few cellular elements contained long, spindle-shaped nuclei. The softer portions of the tumor (fig. 2B) were composed of a very cellular tissue, consisting mostly of large spindle cells with oval nuclei containing a moderate amount of chromatin. Among these there were also strikingly large cells, with dark, bizarre nuclei, and giant cells with several paler nuclei. Between the cells there was a network of rather thick connective tissue fibers, which in places were collected in condensed areas that contained few cells.

Furthermore, there were portions (fig. 2C) in which there was developed a delicate, light blue ground substance between the cells. The tumor cells in these regions often showed stellate form, with long, drawn out cytoplasmic processes.

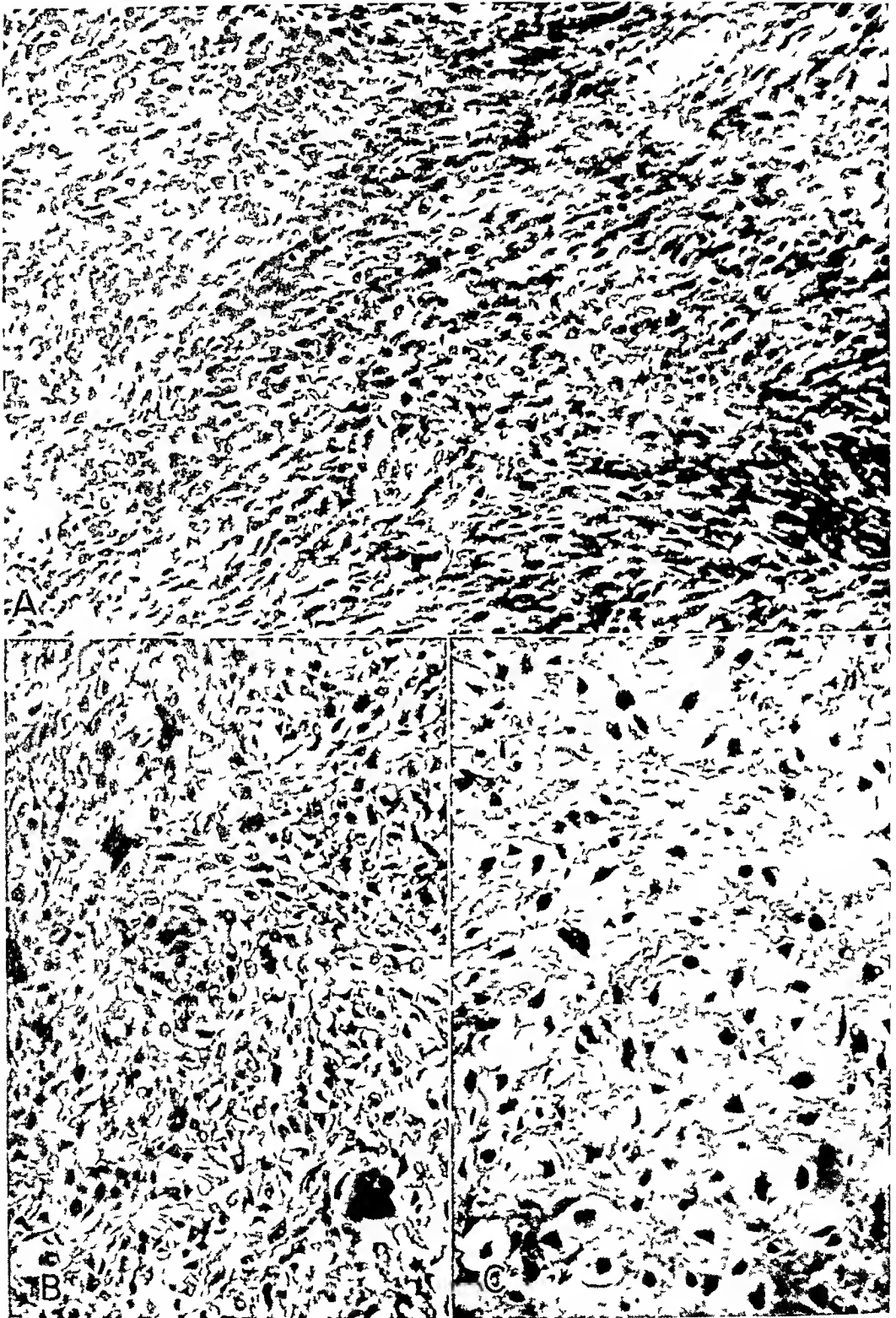


Fig 2 (case 2) —*A*, specimen removed in 1926, representing a fibroblastic sarcoma showing uniformity of cellular structure, *B*, specimen removed in 1930, containing this area showing irregularity of cells and tumor giant cells, *C*, same as *B*, showing an area of myxosarcoma

There was a considerable number of mitotic figures in the cellular portions of the tumor. In the periphery of the tumor there were several areas of necrosis of the tumor tissue.

Diagnosis—The diagnosis was polymorphous spindle cell sarcoma with areas of myxosarcoma.

CASE 3—History—G. E., a woman, aged 50, a housewife, was admitted to the hospital on March 7, 1929. She had been admitted the first time on March 21, 1919, with a history of cough, expectoration and dyspnea of twelve years' duration. For three years, she had noticed occasional blood-tinged sputum. For two months, she had complained of epigastric distress and a striking beneath the sternum. Her condition was diagnosed as aortic aneurysm and bronchial asthma. On her second admission two and a half years later, her condition was the same. Roentgen examination revealed a large, round shadow in the right side of the chest, which was interpreted as a sacculated aneurysm of the first portion of the aorta. The patient was again seen in May, 1925, with the same picture. On her fourth admission, in April, 1926, she was found to be markedly dyspneic and orthopneic. Because of the persistence of the shadow in the right side of the chest over so long a period it was suggested that it might be a dermoid cyst of the mediastinum. At her fifth and last admission, dyspnea was extreme, and there was marked cyanosis. Roentgen examination showed that the shadow had grown considerably. Pulmonary edema developed and the patient died.

Autopsy—Autopsy was performed nine hours later by Dr. Rabin. The body was that of a middle-aged white woman. The face was intensely cyanosed. There were prominent veins over the upper part of the abdomen and lower part of the chest. The lower extremities were very edematous. Owing to the limitations placed on the autopsy in the permit, the viscera were removed en masse through an abdominal incision. Therefore, no adequate description of the thoracic viscera in situ can be made.

The right side of the diaphragm extended to the sixth intercostal space. The right side of the pleural cavity contained a large amount of amber-colored, clear fluid. There were a number of fine fibrous bands between the upper lobe and the wall of the chest, the middle and upper lobes were fused by adhesions. Arising from the mesial aspect of the right upper lobe on a broad base and projecting into the pleural cavity, there was a large whitish, oval tumor covered with a smooth membrane (fig. 3). It measured 19 by 10 by 10 cm. and was firm in consistency, giving the sensation of deep fluctuation. The tumor lay between the lung and the anterior mediastinal structures. Its upper pole extended to the dome of the pleural cavity and the lower pole almost to the diaphragm. The superior vena cava was compressed by the tumor, the ostium of the azygos vein was obliterated and represented by a dimple in the superior vena cava. The entire lung was displaced laterally and posteriorly, the upper and middle lobes being completely atelectatic. The capsule of the tumor was smooth and glistening and was continuous laterally with the pleura of the right upper lobe. In this region, compressed pulmonary tissue was visible beneath the capsule which was reflected from the mesial portion of the lobe onto the tumor for a distance of 3 or 4 cm. On the mesial and anterior surface, a thin patch of anthracotic lung tissue, measuring 11.6 by 3 cm., was seen beneath the capsule. Its continuity with the upper lobe could not be traced. The capsule covering the tumor was reflected mesially over the mediastinum and was continuous with the mediastinal pleura. Therefore, the free surface of the tumor was covered by pleura. Posteriorly, the neoplasm

bulged into the substance of the right upper lobe, from which it was sharply demarcated and could be separated with ease. At the hilus of the lung, however, a small portion of the tumor had forced its way between the bronchial cartilages into the lumen of the bronchus of the upper lobe to form a smooth polypoid projection covered with bronchial mucous membrane. This measured 1.5 cm in length, 1 cm in width, and 6 mm in height. It pointed upward toward the bifurcation, totally occluding the lumen of the bronchus of the upper lobe and slightly narrowing the lumen of the bronchus of the lower lobe. The bronchi distal to the tumor contained mucopurulent material, but were not dilated. On section, the tumor was solid throughout and had a pinkish-gray, fleshy appearance,



Fig 3 (case 3) —Anterior view of the thoracic viscera, showing large tumor on mesial surface of right upper lobe with an area of flattened anthracotic lung tissue on the anterior surface. Note the hypertrophy of the right ventricle.

with many firm, ill defined nodules of firmer consistency. There were a few small yellow, dry areas of necrosis. The bronchial lymph nodes showed a few areas of calcification. The left lung was large and well aerated.

The apex of the heart was formed mainly by the right ventricle, which was markedly hypertrophic and dilated. The pulmonary artery and its branches showed a considerable degree of atherosclerosis. The aorta showed numerous atherosclerotic patches.

The abdomen contained no free fluid. The abdominal viscera were markedly congested.

Microscopic Examination of Tumor—Under low power magnification (fig 4), the tumor appeared to consist of an edematous tissue, rich in fibers, beset with numerous veins and capillaries and very rich in cellular elements. The cells were in part uniformly distributed, in places, they were gathered together in small nests (fig 4A). There was a dense network of parallel and intersecting wavy fibers, which were occasionally collected in loose bundles, especially about the blood vessels, which were surrounded by a mantle of longitudinal fibers. The fibers stained red with van Gieson's stain, blue with Mallory's aniline-blue-fuchsin, and reddish brown with phosphotungstic acid hematoxylin. Prominent among the cells were spindle-shaped elements with long drawn out cytoplasm and elongated oval nuclei with infolded nuclear membranes and a scanty fine chromatin network containing small nucleoli. These could easily be identified as fibroblasts. They were uniformly distributed over the entire section and lay in close relationship to the collagen fibers, to which they were often closely attached. Often the fibers seemed to be continuous with the finely drawn out cytoplasm. These cells were often very large, with several protoplasmic processes and bizarre, remarkably large nuclei, and occasionally there were multinucleated giant cells.

Between the fibers there were often found cells, either singly or in loosely connected groups, of a round or oval shape averaging from 8 by 8 to 8 by 16 microns, with abundant basophil, vacuolated cell bodies (Fig 4C). These were often acidophil about the eccentrically situated nuclei. The nuclei were small and round, measuring 2.5 microns in diameter. They contained distinct, coarsely granular chromatin, which occasionally was gathered about an indistinct nuclear membrane. Occasionally the cells showed pseudopodia-like processes. Often they contained two nuclei.

Furthermore, there were small cells with very dark, round nuclei and narrow cytoplasm, which could be identified as lymphocytes, in addition to a moderate number of eosinophil leukocytes, myelocytes and scattered nucleated red blood corpuscles, singly and in groups. Numerous capillaries in longitudinal and cross-section, and only a few larger veins completed the picture. Attached to the walls of the blood vessels there were occasional spindle-shaped cells with large spindle-shaped nuclei and scanty cytoplasm, having the appearance of fibroblasts, differing from them, however, by their somewhat darker nuclei and indistinct cell bodies.

Doubt as to the nature of the various histologic elements of this tumor can arise only as to the large round cells with abundant cytoplasm. A discussion of these cells is of importance because of their relation to the genesis of this neoplasm.

Although these cells resembled the mononuclear wandering cells of inflamed tissues (polyblasts of Maximow), they can scarcely be considered as such for a number of reasons. Sections of all parts of the tumor contained these cells in great numbers. In general, they were not found to lie in particular proximity to the blood vessels. The latter were not congested nor did they contain many leukocytes. There were no collections of emigrated blood cells in the tissues about the blood vessels. Moreover in their morphology, the cells coincided exactly with the histiocytic wandering cells of embryonic connective tissue. This is shown by a comparison of their characteristics with the description

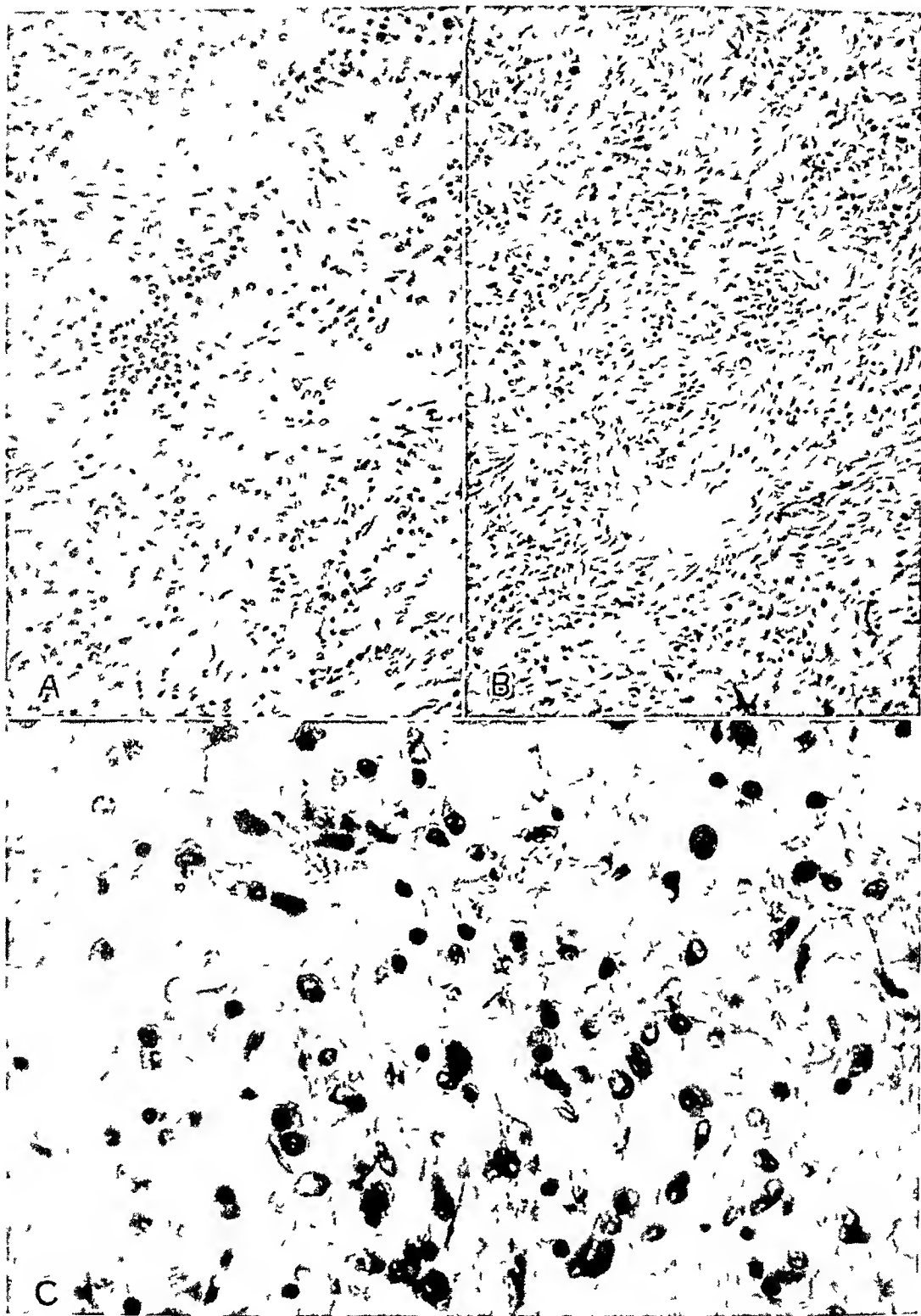


Fig 4 (case 3) — *A* and *B*, low power views showing loose connective tissue containing a variety of cells, *C*, high power view showing fibroblasts, lymphocytes, connective tissue fibers and mononuclear cells, resembling histiocytic wandering cells. Note the resemblance to embryonal connective tissue.

of the latter by Maximow²⁹ (Das Aussehen des lockeren Gewebes bei Embryonen in der mittleren Periode der Schwangerschaft erinnert sehr an entzündetes mit Polyblasten infiltriertes Gewebe des Erwachsenen) (The appearance of the loose tissues in embryos during the middle period of pregnancy reminds one of inflamed tissues, infiltrated with polyblasts, in adults)

The spindle cells described as resembling fibroblasts, lying in the vicinity of the blood vessels, resembled, in their localization and morphology, the undifferentiated perivascular mesenchymal cells of Maximow

The cellular elements of the tumor in their morphology and in their arrangement throughout the stroma bore the closest resemblance to the loose connective tissue in the latter phases of embryonic life

It is therefore justifiable to conclude that the tumor represents a neoplastic overgrowth of embryonic connective tissue. In this respect, it differs from the ripe fibroma, which structurally simulates mature connective tissue. However, it differs from the fibroblastic sarcoma in that it retains the typical structure of the mother tissue in contradistinction to the atypism of malignant connective tissue tumors

CASE 4—*History*—R. M., a white man, 41 years of age, was admitted to Mount Sinai Hospital on Sept. 6, 1919, complaining of pain in the right side of the chest. The physician had aspirated the right side of the chest and withdrawn some bloody fluid. On admission to the hospital, the patient was dyspneic and on examination showed dilated venules over the right side of the lower part of the chest. There were signs of fluid in the right side of the chest. The edge of the liver was felt three fingers below the costal margin. Roentgen examination showed a large shadow almost completely filling the right side of the chest, presenting the appearance of a neoplasm. The patient was readmitted in April, 1930, complaining of increasing dyspnea and orthopnea. Examination showed the same signs as before. The liver was, however, larger, extending 15 cm. below the costal margin. The patient was intensely cyanosed. The lower extremities were very edematous. There were varicose veins over both thighs. The patient died, two days after admission to the hospital, of cardiac failure.

Autopsy—Autopsy was performed nine hours later by Dr. Otani. The body was that of a middle aged man, slightly obese, in complete rigor mortis. There was marked cyanosis of the head and neck, with slight clubbing of the fingers and toes. There was no edema. The thoracic organs had to be removed through an abdominal incision, and no direct inspection of the thoracic viscera in situ was possible. The right side of the diaphragm extended to the sixth, the left to the fifth, interspace. The right side of the chest was filled by a soft tumor mass exceeding the size of a man's head, which was adherent to the parietal pleura of the anterior and lateral walls of the chest. There was a thick band between the tumor to the inferior border of the middle lobe. The mass measured 25 by 19 by 12 cm. and was shaped like a cast of almost the entire right pleural cavity.

²⁹ Maximow, A., in Moellendorff, W. *Handbuch der mikroskopischen Anatomie des Menschen*, Berlin, Julius Springer, 1927, vol. 2, pt. 1, p. 504.

with the exception of the dome, which was occupied by the compressed upper lobe. It was encapsulated by a smooth fibrous membrane that was continuous with the visceral pleura of the right lower lobe (fig 5). It was connected with the anterior portion of the inferior border of the lower lobe by a flat pedicle of lung tissue, 6 cm in breadth, 5 cm in length and 6 mm in thickness. The lung tissue of this pedicle continued for a distance of about 10 cm as a gradually thinning shell over the posterior surface of the tumor beneath the pleural capsule. The tumor developed in front of the lower lobe. Its base rested on the diaphragm. Its upper pole displaced the upper and middle lobes into the dome of the pleura. It grew between the lobes in the large fissure, the upper and the middle lobe resting on the front of the cranial portion of the tumor. Arising in a similar manner from the base of the lower lobe was a tongue-shaped second tumor

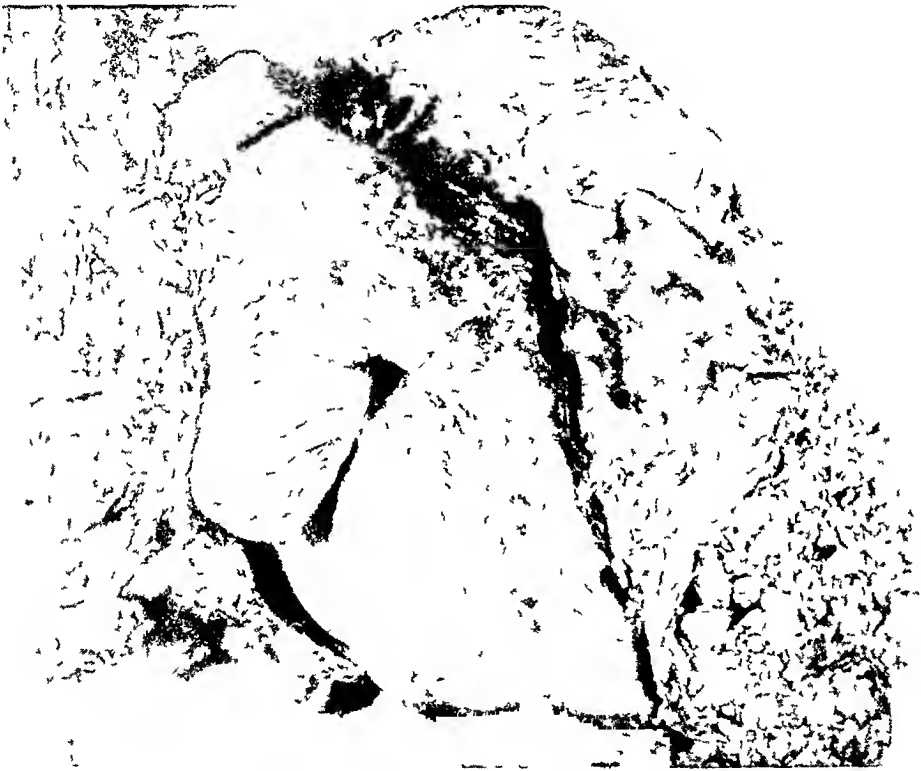


Fig 5 (case 4)—Posterior view of right lung, showing large and small lipomas arising from the subpleural areolar tissue and attached to the lower lobe by pedicles of lung tissue

measuring 7.5 by 4 by 2.5 cm. This also was covered by pleura reflected from the lower lobe, and showed beneath the pleural capsule a continuation of pulmonary parenchyma for a short distance from its point of origin. On section, both tumors were composed entirely of grapelike nodules of yellow fat tissue (fig 6). It was richly vascularized by wide sinuses filled with coagulated and liquid blood, which were continuous with the pulmonary blood vessels.

The left pleural cavity contained no fluid, and the lung was free from adhesions. It was slightly compressed from the displacement of the mediastinal structures to the left side by the tumor occupying the right pleural cavity.

The upper portion of the parietal pericardium on the right side was adherent to the tumor. The pericardial sac was empty. The heart weighed 480 Gm. The

apex was formed by the right chamber. The right ventricle showed an extreme degree of hypertrophy and dilatation. The right auricle was markedly dilated, the tricuspid ring was very wide. The pulmonary artery measured 7.5 cm. at its point of origin and showed slight atherosclerosis. The left ventricle was slightly hypertrophic. The valves of the heart were free from changes.

The abdominal viscera showed marked congestion.

Microscopic Examination of Tumor—Microscopic examination of the tumor showed the typical structure of a lipoma.

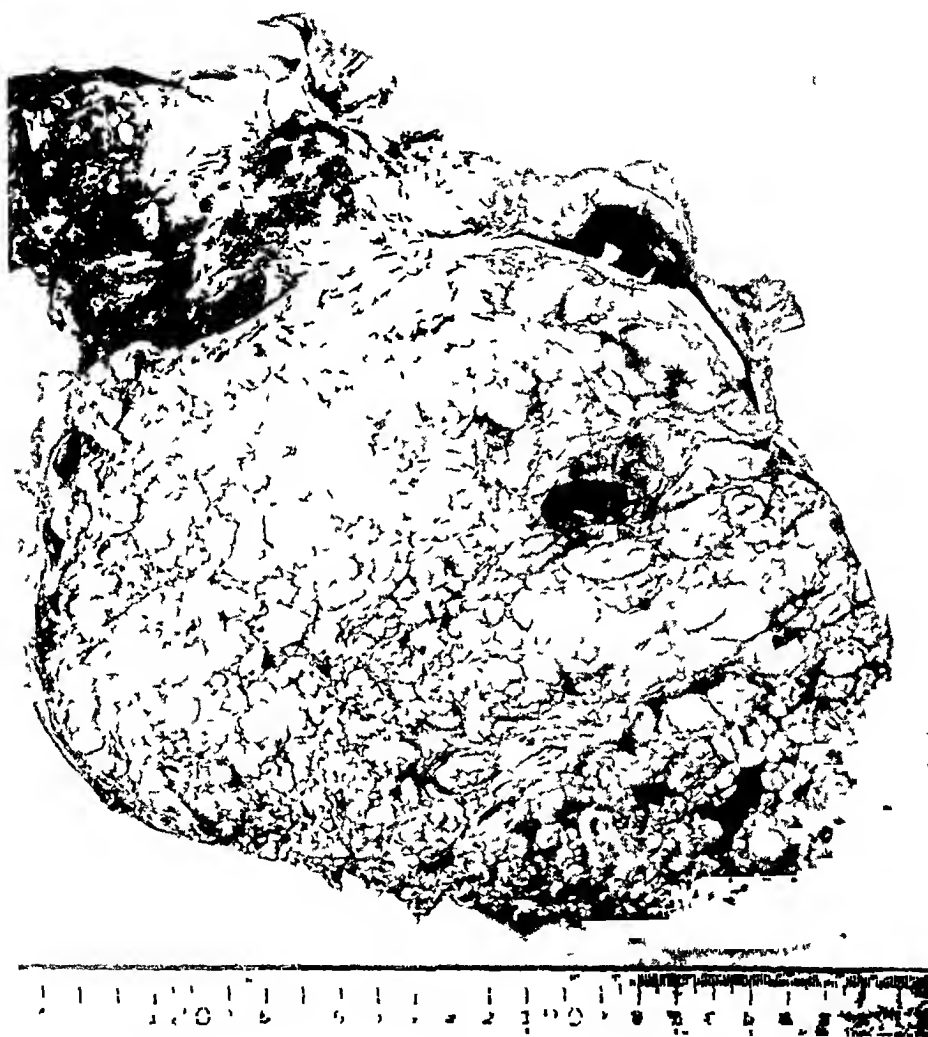


Fig. 6—Same tumor as in figure 5 on cross-section, showing typical appearance of lipoma.

COMMENT ON CASES 1 TO 4

In their slow progress and their gross anatomical features, because of which they are designated as giant tumors of the pleura, these cases conformed with the cases in the literature. In three of the cases, the localization of the tumor, as a pedunculated mass projecting into the pleural cavity and covered everywhere by the visceral pleura, showed

conclusively the point of origin of the neoplasm to be the subserous pleural tissue. At the point of attachment of the tumor, the lung was drawn out in a pedicle that spread out over the tumor for a short distance, but was separated everywhere by the tumor capsule. In the two fatal cases, death was due to the mechanical interference with the pulmonary circulation caused by the enormous tumor, resulting in failure of the right ventricle.

The microscopic examination of these growths, in accordance with the other observations in the literature, showed them to be of mesenchymal origin. There were, however, differences in the type of tissue of which they were formed. The first three were connective tissue tumors. The first was a fibroblastic neoplasm of great cellularity. The tumor cells were uniform in type and showed no mitotic figures. The occasional infiltration of the capsule, however, indicated that the tumor possessed malignant properties, and fibrosarcoma of a low grade of malignancy was diagnosed. It is significant that the second, at its first examination, showed a similar picture. Specimens of the tumor removed four years after the partial resection of the neoplasm showed remarkable changes in the histology, indicating a highly malignant character, which was also evidenced by the formation of metastases in the other lung. It is possible that the repeated surgical interference in removing portions of the tumor was responsible for the malignant transformation of the tumor. This has been observed commonly after incomplete removal of certain fibroblastic tumors. Intensive radiotherapy did not arrest the further growth and dissemination of the neoplasm.

The third tumor, however, in spite of its embryonal histologic structure, was benign. As has been stated, the microscopic appearance of the tumor conformed fully with that of embryonal connective tissue in the later stages of its development. It did not show any qualitative aberration from this tissue, and the quantitative proportions of the cellular elements and fibrillar structures were identical with those of normal embryonal connective tissue of this phase. The long clinical course of at least twenty years' duration and the absence of any infiltration of the surrounding tissue confirmed the benign nature of the growth.

The fourth tumor was a simple lipoma, which caused death merely because of the tremendous proportions to which it had grown. Although there are no reports of giant fatty tumors of the visceral pleura in the literature, the origin of such a tumor from the subserous areolar tissue of the visceral pleura is not surprising. The development of fat tissue in the edges of the lung in obese patients is not uncommon. Its significance in relation to the histogenic potentialities of the undifferentiated

perivasculai mesenchyme in this region has been commented on by Wassermann³⁰ in his elaborate study on the development of fat tissue

DIFFUSE PLEURAL NEOPLASMS

Since the first description by Wagner³¹ in 1870, there has arisen a controversy concerning the oncology of primary diffuse pleural neoplasms, which has grown with succeeding case reports and has lasted to the present day. The lack of agreement regarding the classification of these tumors has been caused by the wide variations in the appearance of the growths both grossly and microscopically. Some appear as epithelial growths, others as of connective tissue origin, and others seem to belong to neither class or to both. Whether the point of origin lay in the superficial lining cells of the pleura (mesothelium), in the subserous connective tissue or in the lymphatic endothelium has been a source of dispute. This, together with the polymorphic picture, has given rise to confusion, illustrated by the varied nomenclature which has been applied to these tumors. Krumbein³² collected thirty different names for the tumors under discussion in his exhaustive study of the reported cases. The names applied most frequently, endothelioma, endothelial carcinoma, carcinoma, sarcoma, lymphangitis proliferans, sarco carcinoma and mesothelioma, are indicative of the different morphologic pictures and of the different opinions of authors as to the point of origin. To make this confusion more complete, there have been included in the literature on primary tumors of the pleura a number of cases that, on critical examination, are proved to originate definitely in the lungs or in the bronchi.

This situation was clarified to a considerable degree by the critical review of all the cases in the literature by Robertson³³ in 1923. From an independent review of the literature we conclude, as did Robertson, that a considerable proportion of the cases reported were really cases of metastatic tumors of the pleura, and that all tumors of the pleura should be considered as metastatic if there is present in one of the viscera a neoplasm that can be considered a primary neoplasm. The belief in the nonexistence of "endothelioma" arising from the subserous lym-

30 Wassermann, F. Die Fettorgane des Menschen, *Ztschr. f. Zellforsch. u. mikr. Anat.* **3** 235, 1926.

31 Wagner, E. Das tuberkelähnliche Lymphadenom, *Arch. f. Heilk.* **11** 497, 1870.

32 Krumbein, C. Ueber die Natur der Deckzellen der serösen Haute-Untersucht an Hand eines primären Pleuracarcinoms, *Virchows Arch. f. path. Anat.* **249** 400, 1924.

33 Robertson, H. E. Endothelioma of the Pleura, *J. Cancer Research* **8** 317, 1923-1924.

phatics is also concurred in. However, we disagree with the extreme point of view that no tumor of an epithelial structure can originate primarily in the pleura, and that the serosal lining cells cannot be the source of such tumors.

A case which has come under our observation showed structural peculiarities that are of interest in this connection.

REPORT OF CASE

History—R. Z., a woman, 26 years old, was admitted to Mount Sinai Hospital on Aug. 22, 1929, complaining of pain in the left side of the chest from which



Fig. 7 (case 5) —Anterior view of the thoracic viscera, showing diffuse growth of a mesothelioma of the left pleura. The heart has been reflected to the right in order to show the infiltration of the pericardium.

she had suffered for a period of eleven months. Because of this ailment, she had been admitted to another hospital, where a rib resection was performed and radiotherapy advised. She subsequently received seven treatments at another hospital. On admission, she was weak and dyspneic. She had a temperature of 102° F. The left side of the chest was very prominent, the intercostal spaces obliterated. There was flatness to percussion over the entire left side of the chest, with the exception of the left apex, anteriorly, where the percussion note was tympanic. Breath sounds were absent. The heart was displaced to the right side, the right border was situated 3 inches (7.5 cm.) to the right of the midline. The spleen was

palpable about 2 cm beneath the left costal margin. Roentgen examination of the chest showed a diffuse shadow over the entire left pulmonary field, with a marked displacement of the heart to the right side. An exploratory puncture was performed. The needle met with great resistance. No fluid was obtained but a small piece of tissue was withdrawn with the aspirating needle. The diagnosis made at this time was that of a neoplasm of the pleura.

Microscopic examination of the fragment of tissue showed it to be composed of irregular spindle cells with intercellular fibrous stroma. The cells varied in size, shape and staining capacity. Most of the nuclei were spindle-shaped. However, some were more rounded and irregular. In general, the nuclei contained

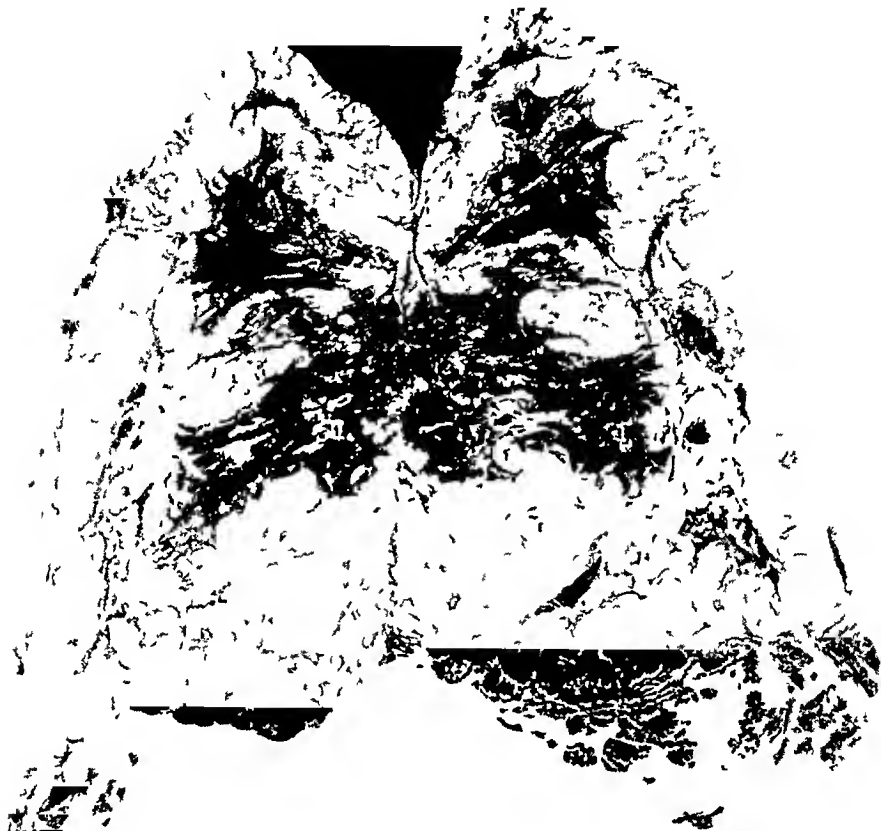


Fig 8 (case 5) —Coronal section showing the complete encasement and infiltration of the lung by tumor

finely divided chromatin with a distinct nuclear membrane. The diagnosis from this histologic specimen was fibrosarcoma.

The course was rapidly downhill. The patient became weaker, her fever persisted, and she became increasingly anemic. She was given an injection of Coley's vaccine. Three days later her temperature rose very sharply to 109 F, and she died.

Autopsy—Necropsy was performed on Sept 10, 1929, by Dr S. Otani. The body was that of a well developed and fairly well nourished white woman. The left side of the chest bulged forward markedly and was resistant to pressure. The mucous membranes were pale. There was slight cyanosis of the face. The fingers and toes showed no clubbing. There was a scar of an old rib resection

in the posterior portion of the left side of the chest. There was a small, but deep decubitus ulcer over the sacrum, with bone exposed. The diaphragm rested at the fifth rib on the right side and at the sixth rib on the left side.

Owing to a limitation of the permission for necropsy, the organs were removed through an abdominal incision, therefore, no exact observations could be made of the intrathoracic situs. There were about 40 cc of clear fluid in the right side of the chest and a few fibrous adhesions over the middle and upper lobes. The right lung showed some collapse of the lower lobe. There was a small, whitish nodule in the pleura of the middle lobe. The left side of the pleural cavity was entirely obliterated, but it was possible to separate the lung from the wall of the chest. The parietal pleura was fused with the visceral layer, except at the base. It was composed of nodular tumor tissue which infiltrated the diaphragm and the wall of the chest between the ribs, especially in the region of the operative scar. The left lung was completely ensheathed by firm, nodular, whitish, fibrous tumor tissue which measured from 4 to 15 cm in thickness, the entire mass weighing about 4 Kg (fig 7). It measured 30 cm in the longitudinal, 17 cm in the frontal, and 15 cm in the sagittal, diameters. The tumor infiltrated the periphery of the lung extensively in an irregular manner, in places extending into the center of the lung. On various coronal sections, the lung parenchyma appeared compressed and extremely irregular in outline because of the extensive invasion by neoplasm (fig 8). The bronchi showed neither infiltration nor narrowing of the lumen. The lymph nodes at the hilus of the lung were slightly enlarged and anthracotic, on section, some showed infiltration by white tumor tissue.

The posterior portion of the parietal pericardium was encased and infiltrated by tumor nodules. The pericardial cavity measured 13.5 cm in its long axis and 10 cm at its widest portion. The heart was small and atrophic and displaced to the right. The epicardium was covered with a fine fibrinous exudate. The columnae carneae of the left ventricle were markedly flattened and the papillary muscles atrophic. The arch and thoracic portion of the aorta were firmly fixed by the tumor and slightly narrowed.

The peritoneal surface of the left portion of the diaphragm showed nodular infiltration by the neoplasm, which involved the retroperitoneal tissues in this region and surrounded the left suprarenal capsule and the upper portion of the left kidney. There was no fluid in the peritoneal cavity.

The weight of the liver was 2,570 Gm. It showed marked congestion, but no metastases.

The weight of the spleen was 300 Gm. It was about twice the normal size and firm in consistency. The capsule showed a number of scattered white plaques. The pulp was congested.

Each kidney weighed 200 Gm. The capsule of the left kidney showed infiltration by the tumor. The capsule on both sides stripped easily, revealing smooth surfaces. There was no infiltration of the kidneys by tumor tissue.

The left suprarenal gland was surrounded by tumor tissue, but not infiltrated. The right showed no abnormality.

The uterus showed a small, white, fibrous nodule on the fundus. The endometrium was smooth and pale. The ovaries and tubes appeared normal.

The structure of the pancreas was natural, the consistency firm. No evidence of tumor was seen.

The gastro-intestinal tract was normal.

Microscopic Examination of Tumor—Sections were taken from various portions of the tumor, including the infiltrated lung. Sections were also taken of the lining of the pleural cavity in order that a search might be made for the pleural mesothelium. The latter was absent. The section showed only tumor tissue, the surface of which was necrotic and covered by fibrin.

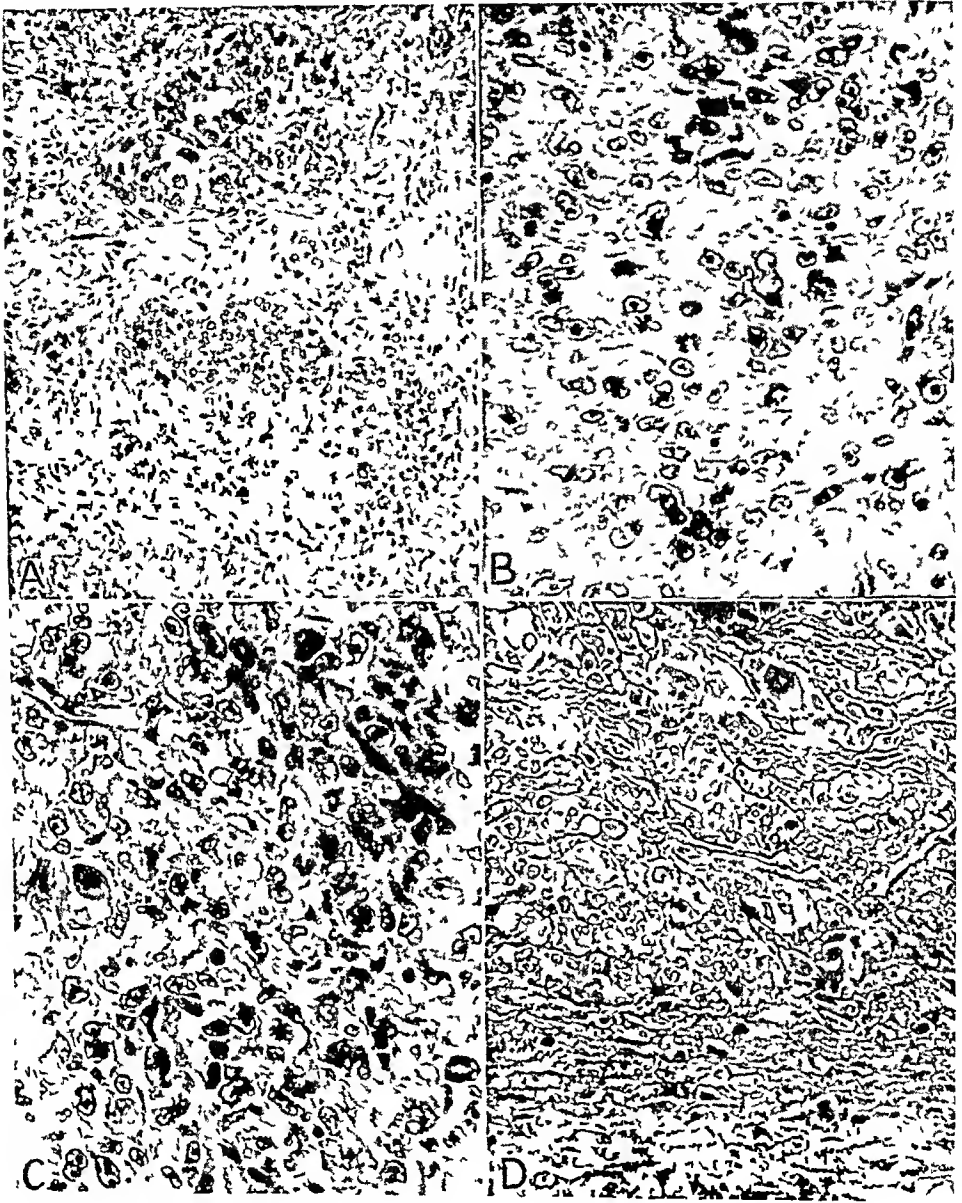


Fig 9 (case 5)—Microscopic sections illustrating the epithelial nature of portions of the tumor. *A*, cells arranged in nests, *B*, epithelial characteristics, polygonal cells with abundant cytoplasm and vesicular nuclei with large nucleoli, arranged in rows, *C*, same cell characteristics as in *B*, and, in addition, coarse mitotic figures. *D*, Mallory's stain showing intercellular fibers between epithelial-like cells and multinucleated tumor giant cells.

The material was fixed in Zenker-Helly's solution and formaldehyde, and was embedded in paraffin. The sections were stained with hematoxylin-eosin, and by van Gieson's, Mallory's aniline blue-fuchsin, the phosphotungstic-hematoxylin and the Bielschowsky-Maresch silver impregnation methods.

Various portions of the tumor showed different characteristics. In general, the tumor was composed of irregular cells with large nuclei (fig 9B and C). The

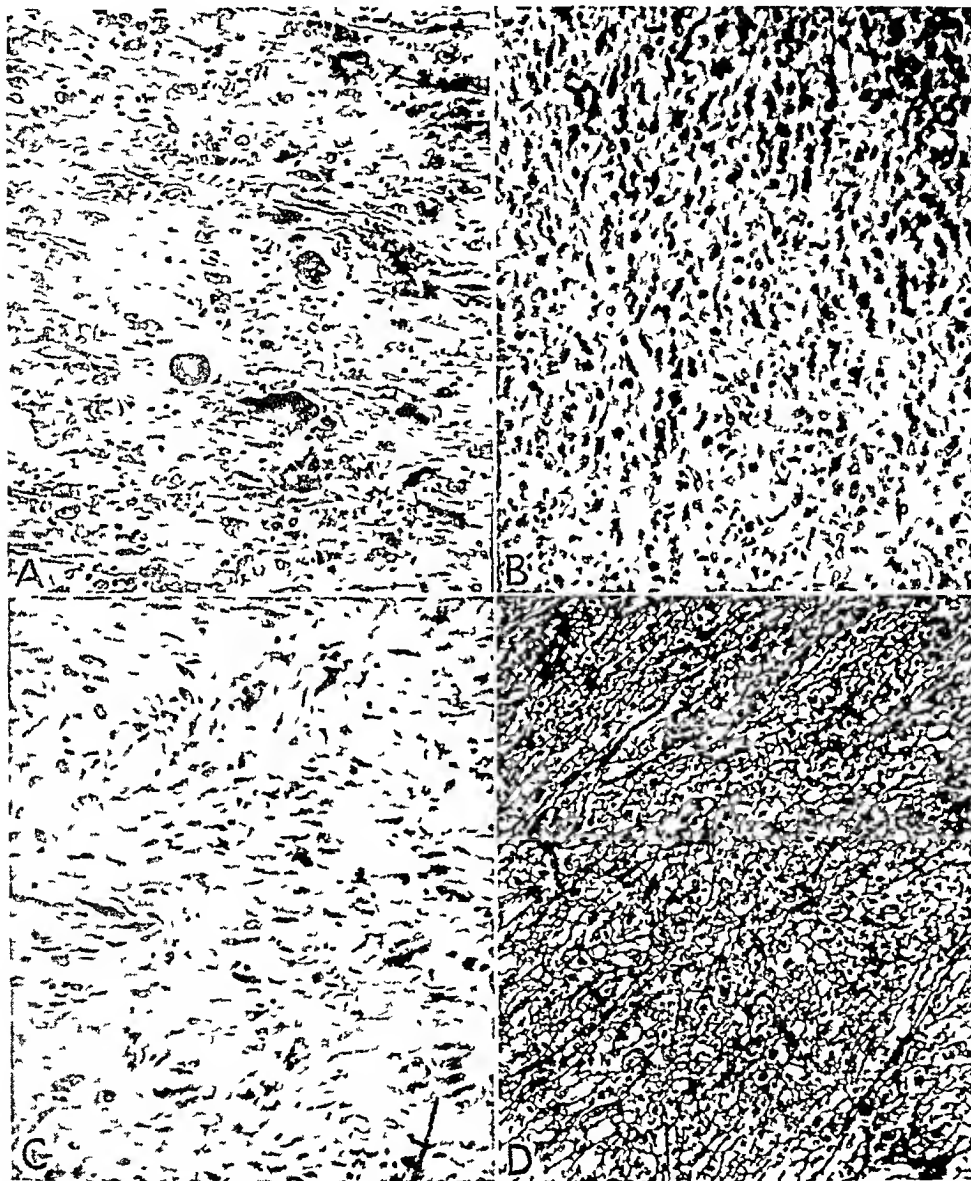


Fig 10 (case 5)—Microscopic sections illustrating sarcomatous portions of tumor. *A*, polymorphous appearance of elements with large atypical giant cells and abundant stroma, *B*, fibroblastic appearance of tumor cells in a cellular area, *C*, flattened cells of fibroblastic appearance with dense stroma, *D*, Bielschowsky stain showing fibers surrounding each cell.

cells varied considerably in size, from 11 by 7 to 21 by 12 microns, with nuclei varying from 7 by 7 to 15 by 10 microns. In places, the cells were flattened and in other places rounded. The nuclei also varied in size and shape. They pos-

sessed a sharp nuclear membrane, which was often infolded. The nuclei were pale. The chromatin network was scanty. The nuclei contained one or more distinct nucleoli (fig 9*B*). Some of the nucleoli were exceedingly large. Many of the cells contained two or more nuclei of the same appearance. There were many coarse mitotic figures (fig 9*C*). The cytoplasmic outline was very hazy. There were fine cytoplasmic processes, which, in the specimen stained with hematoxylin-eosin, seemed to blend with intercellular fibers.

The cells also varied in their arrangement. In some sections there were areas in which the cells were closely approximated with scant intercellular material. This, together with the characteristics of the nuclear structure, gave the appearance of an epithelial new growth. In places, the cells lay in nests, forming an alveolar arrangement (fig 9*A*). In other places, they were arrayed in rows, a trabecular arrangement. Here also the arrangement of the cells and the nuclear structure gave the appearance of an epithelial growth (fig 9*B*).

In sections stained by the Mallory aniline-blue method or impregnated with silver according to Bielschowsky-Maresch, a network of fibers surrounding almost every cell was demonstrated (fig 9*D*). In order to trace the origin of the fibers, the nests of tumor cells within the adjacent lung tissue were examined. Here not every cell was surrounded by fibers. However, the cytoplasm of some of the cells showed a bluish violet tint (with Mallory's aniline-blue stain), and occasionally one could recognize bluish specks within the cytoplasm with a condensation of bluish material at the edges of the cells. Such an appearance was not found in the cells that were surrounded by fully developed fibers.

In places, the cells assumed a bizarre form (fig 10*A*). They were very irregular, and there were many multinucleated giant cells, with considerable fibrillar tissue between the cellular elements. There were, in addition, a number of thin-walled capillaries and occasional flattened fibroblasts.

In other places, the cells were markedly flattened and elongated (fig 10*B* and *C*). The nuclei also were flattened and elongated, and the chromatin network was compressed and appeared more compact, giving the nuclei a darker appearance. The infolding of the nuclear membrane was more prominent in these regions. In these portions the fibers, which were more scanty and formed only an incomplete network in the other portions of the specimen, were numerous. Wavy fibers, 1 micron in thickness and running longitudinally, were seen between the cells.

In the section impregnated with silver, the fibers were seen everywhere between the cells (fig 10*D*). In places, the fibers were condensed to form thick bands. Here the cells were compressed and fewer in number.

COMMENT ON CASE

This case belongs to the group of diffuse pleural neoplasms which completely ensheath the lung. Its primary origin in the pleura is beyond question. Although the autopsy was limited to the abdomen and thoracic viscera, there was no clinical suspicion throughout the entire course of the illness of any new growth in any other region of the body. In the organs that were examined there was no other growth that could possibly have been considered as primary. Moreover, the histologic picture conformed fully with that of some of the undoubted primary pleural tumors described in the literature.

The striking peculiarity of the histologic picture was the fact that it was composed of cells of an epithelial appearance, which, however, were almost everywhere separated from each other by collagen fibers. In places these cells were arranged in alveolar nests or in rows, with only a scanty incomplete fibrillar network. In other places, however, the cells were remarkably flattened, with a marked development of intercellular tissue, giving the appearance of fibroblastic tissue. The intercellular fibers appeared to be formed by the tumor cells themselves. This was indicated by the absence of other fiber-forming cells and by the observation of fibril development within the cytoplasm of the cells situated in the peripheral portions of the tumor.

The predominant cell type was a large polygonal cell, often with abundant cytoplasm. The nucleus was large. The chromatin was sparse and finely divided, giving the nucleus a pale vesicular appearance. The chromatin was condensed at the periphery of the nucleus, forming a very distinct nuclear membrane which was irregular and infolded. There were many large nucleoli. In spite of the presence of the intercellular fibers these cells generally differed from fibroblasts. The appearance was more that of epithelial cells, and it corresponded to the description of the serosal lining cells as given by Maximow.²⁹

Among the primary pleural neoplasms described in the literature there are a number the descriptions of which are similar to that of the one reported here. Cases of such tumors have been reported by a number of observers. Bernard³⁴ and Gutmann³⁵ gave excellent descriptions of the epithelial-like nucleus and of the reticulum which surrounded each cell. They appreciated the peculiar nature of the tumors and each considered his case unique in the literature. Kornitzer³⁶ regarded his case as that of simple endothelioma in spite of the fact that his description is identical with that given here. Podack³⁵ and Boehme³⁷ remarked that their tumors contained islands of epithelial cells, but also showed sarcomatous qualities. They concluded, however, that they were dealing with a proliferation of lymphatic endothelium, which is closely related to the mesenchyme. The case reported by MacMahon and Mallory³⁸ as a pleural sarcoma is found, on examination of their plates, to simulate

34 Bernard, cited by Robertson (footnote 33)

35 Gutmann, C. Beitrag zur Kenntnis der primären malignen Tumoren der Pleura, *Deutsches Arch f klin Med* **75** 337, 1902-1903

36 Kornitzer, E. Zur Kenntnis der Pleuratumoren, *Berl klin Wchnschr* **56** 1039, 1919

37 Boehme, M. Primäres Sarcocarcinom der Pleura, *Virchows Arch f path Anat* **81** 181, 1880

38 MacMahon, H. E., and Mallory, G. K. Fibrosarcoma of the Pleura, *Am J Path* **4** 387, 1928

our case very closely. Glockner's³⁹ two cases of endothelioma of the peritoneum prove to be of a similar nature.

That the pleural lining cells are capable of producing tumors with both epithelial and connective tissue characteristics was pointed out by Paltauf,⁴⁰ Borst⁴¹ and Kaufmann.⁴² Miller and Wynn,⁴³ in reporting a case of tumor of the peritoneum, were the first to advance the opinion that a neoplasm of the lining cells was able to present both epithelial and fibroblastic characteristics, because of the embryologic relationship of these cells to the mesoderm. This opinion was also held by Zeckwer⁴⁴ in her report of a case of pleural mesothelioma. A consideration of the embryonal development and of the recent investigations of the potentialities of the mesothelial cells corroborates this view.

According to the accepted embryologic studies of Heitwig, the lining of the pleuropericardial cavity develops from the celomic epithelium, which is developed by the splitting of the mesoderm (not the mesenchyme as is stated by Kaufmann, who is quoted by Robertson³³). There is no basement membrane between this celomic epithelium and the underlying mesenchyme, which later also arises from the mesoderm and which gives rise to connective tissue, the blood and the endothelium of the lymphatic and blood vessels. The close genetic relationship between the celomic epithelium and the underlying mesenchymal tissue is therefore apparent.

Since this epithelial tissue has its ultimate origin in the mesoderm, and since, as later research has shown, it has potentialities which differentiate it from the ectodermal or endodermal epithelium, it has been called mesothelium. It should be noted that in its development it has no direct relation to the endothelium of the lymph spaces, which is a highly specialized form of mesenchyme.

Early observers believed that they could show transitions from the mesothelial coverings of the pericardium to fibrous tissue. The pictures, however, were not convincing.

Since the work of Marchand⁴⁵ in the production of inflammatory reactions in the peritoneum by the introduction of spores of *Lycopodium*,

39 Glockner, A. Ueber den sogenannten Endothelkrebs der serösen Haute (Wagner-Schulz), Ztschr f Heilk **18** 209, 1897.

40 Paltauf, R. Ueber Geschwulste der glandula carotica, Beitr z path Anat u z allg Path **11** 277, 1892.

41 Borst, M. Die Lehre von den Geschwulsten, Wiesbaden, J. F. Bergmann, 1902, vol 1, p 287.

42 Kaufmann (footnote 4, p 386).

43 Miller, J., and Wynn, W. H. A Malignant Tumor Arising from the Endothelium of the Peritoneum and Producing a Mucoid Ascitic Fluid, J Path & Bact **12** 267, 1908.

44 Zeckwer, I. T. Mesothelioma of the Pleura Arch Int Med **34** 191 1924.

45 Marchand, F. Die Veränderungen der peritonealen Deckzellen nach Einführung kleiner Fremdkörper, Beitr z path Anat u z allg Path **69** 1, 1921.

a controversy has arisen as to the potentiality of the mesothelium for displaying mesenchymal characteristics and for forming intercellular fibers. Marchand⁴⁶ in his early work, which was checked by more careful later observations, believed he was able to demonstrate this beyond a doubt.

Recently, Cunningham,⁴⁷ who has been the chief exponent of the specificity of the mesothelial cells as epithelium, has cast doubt on the conclusions drawn from these studies based on the irritation of the serous membranes by foreign bodies. He was able to show remarkable pictures of hyperplasia of the mesothelial cells by the injection of irritants into the serous cavities. Other authors have called attention to the fact that the mesothelium of lower animals may become so differentiated as epithelial structures that they bear cilia. Stratified epithelial-like proliferations have been noted over the peritoneal surface of the diaphragm and in the beadlike thickenings on the splenic capsule. Cunningham felt that the connective tissue growth that followed irritation of the pleura and peritoneum was due to the degeneration of the serous lining cells and to proliferation of the subserous connective tissue. By using the silver impregnation method to demonstrate what he considered to be the outline of the mesothelial cells, he was able to demonstrate the rounding of these cells, their degeneration, the separation of the cells from each other and the formation of fibroblasts between them. He therefore considered that this fibroblastic proliferation originated from the connective tissue underneath the lining cells and not from the mesothelial cells.

Maximow,⁴⁸ in his latest work, pointed out the difficulty of drawing conclusions from such observations. By means of tissue cultures he was able to observe direct transitions from the mesothelial cells to fibroblasts. The degenerative changes noted by Cunningham were observed, but after a longer or shorter interval of time, the rounded mesothelial cells gradually developed processes, became of fibroblastic appearance and developed collagen fibers.

This constitutes final proof of the mesenchymal potentialities of the mesothelium. These potentialities, proved both by embryologic and by experimental evidence, explain the peculiarities presented by the

46 Marchand, F. Ueber die Beziehungen der pathologischen Anatomie zur Entwicklungsgeschichte, besonders der Keimblattlehre, Verhandl. d. deutsch. path. Gesellsch. **2** 38, 1899.

47 Cunningham, R. S. The Changes in the Omentum of the Rabbit During Mild Irritations with Especial Reference to the Specificity of the Mesothelium, Bull. Johns Hopkins Hosp. **33** 257, 1922, The Effects of Chronic Irritations on the Morphology of the Mesothelium, *ibid.* **35** 11, 1924.

48 Maximow, A. Ueber das Mesothelium (Deckzellen der serösen Haute) und die Zellen der serösen Exudate, Arch. f. exper. Zellforsch. **4** 1, 1927.

tumor which has been reported here. That epithelial structures may develop from the mesothelium in accordance with the observations of Cunningham cannot be denied. The formation of primary epithelial tumors of the pleura as reported by Harris,⁴⁹ Benda,⁵⁰ and Sprunt⁵¹ is explainable on this basis. In fact, the illustrations accompanying the reports of the latter two present a close resemblance to the epithelial hyperplasia produced experimentally by Cunningham.

The occurrence of tumors that present both epithelial and mesenchymal characteristics, as in our case, and in those reported in the literature and referred to here, therefore, is not surprising. Even diffuse sarcomas, such as described by Cohen,⁵² Deruschinsky,⁵³ Schwalbe,⁵⁴ Regnault,⁵⁵ Petriaux,⁵⁶ Oelrick,⁵⁷ and Brandam,⁵⁸ including the chondrosarcomas of Busse,⁵⁹ Schultze⁶⁰ and Fallscher,⁶¹ may conceivably be explained on the same basis of the developmental potentialities of the mesothelial cells. The similarity of these diffuse sarcomas in their gross appearance to the other diffuse pleural tumors makes it probable that they also originate from the surface and not from the subserous areolar tissue. It is to be expected that tumors arising from the surface would be diffusely spread throughout the pleural cavity. On the other hand, tumors arising subpleurally are apt to remain localized. It is significant that the localized neoplasms of the pleura described

49 Harris, T. A Contribution to the Pathology and Clinical Features of Malignant Disease of the Pleura, *J Path & Bact* **2** 174, 1893-1894

50 Benda, C. Ueber das primäre Carcinom der Pleura, *Deutsche med Wchnschr* **23** 324, 1897

51 Sprunt, T. P. Primary Carcinoma of the Pleura, *Bull Johns Hopkins Hosp* **22** 289, 1911

52 Cohen, M. Ein Fall von primärem Fibrosarcoma der Pleura, *Inaug Diss*, Würzburg, 1895

53 Deruschinsky, S. F. Primäres Sarkom der Pleura, *Deutsche med Wchnschr* **14** 52, 1888

54 Schwalbe, E. Zur Lehre von den primären Lungen und Pleurageschwulsten, *Deutsche med Wchnschr* **17** 1238, 1891

55 Regnault, F. Sarcome primitif de la plevre, *Bull Soc anat de Paris* **62** 528 1887

56 Petriaux, L. Reflexions sur quelques cas de tumeurs de la plevre, *These de Paris*, 1893, p. 51

57 Oelrick, I. D. Ueber maligne Lungen- und Pleuratumoren, *Nord med Ark*, 1903, vol. 3 nos. 3 and 8

58 Brandam, J. Contribucion al estudio anatomico-clinico de los sarcomas primitivos de la pleura, *Rev Soc med argent*, Buenos Aires **15** 237, 1907

59 Busse, I. Ueber ein Chondromyxosarcoma pleurae dextrae, *Virchows Arch f path Anat* **189** 1 1907

60 Schultze. Knorpel der Lungenpleura. *Inaug Diss*, Greifswald, 1905

61 Fallscher Karl. Ueber einen Fall von Chondrosarkom der pleura, *Inaug Diss*, Bonn 1909

in the first part of this article all arose subpleurally and were of undoubted connective tissue origin

Most of the difficulty has been due to too much emphasis on the histologic picture and lack of appreciation of the point of origin. This conception of the unitarian origin of the diffuse neoplasms of the pleura eliminates the confusing experiences in classifying pleural tumors. It is therefore recommended that the term mesothelium, the term first applied by Adam, be accepted to designate all the diffuse neoplasms of the pleura that arise from the mesothelium, whether they appear to be composed of epithelium, connective tissue, or both.

SUMMARY

Primary neoplasms of the pleura are divided into localized and diffuse forms. The literature on giant tumors of the visceral pleura has been reviewed, and four new cases have been reported. These tumors are of mesenchymal structure and originate from the subpleural areolar tissue. Although, histologically, they usually present evidences of a low grade of malignancy, they progress very slowly and usually cause death by interference with the pulmonary circulation. They offer an opportunity for surgical removal.

Diffuse neoplasms of the pleura arise from the surface lining cells, the mesothelium, and should be designated mesothelioma. They may present the characteristics of epithelium, of connective tissue or of both. A case of the last type is reported. The complex structure of the tumor is explained by the varied potentialities of the mesothelial cells as shown by their histogenesis and by experiment.⁶²

⁶² After the presentation of this paper, attention was drawn to the article of E. Kru (Zur Kenntnis der primären Geschwulste des Brustfells, *Virchows Arch f. path. Anat.* **272** 650, 1929), who had previously emphasized the significance of the work of Maximow in explanation of three cases of pleural mesothelioma that showed both epithelial and fibroblastic characteristics.

AVITAMINOSIS

I PATHOLOGIC CHANGES IN NURSING AND IN WEANED ALBINO
RATS SUFFERING FROM VITAMIN B DEFICIENCY *

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During the last few years it has been definitely established ¹ that the dietary factor which McCollum and Kennedy ² in 1916 termed "water-soluble B" and which was later generally recognized as "vitamin B" is a complex composed of at least two distinct vitamins one of these is relatively thermolabile and has antineuritic and growth-promoting properties, the other is more stable after heating under pressure also possesses growth-promoting properties, and functions in the prevention and cure of pellagra-like symptoms in the rat. The former is also referred to as the antiberiberi, and the latter as the antipellagic, vitamin. The nomenclature of these dietary essentials has not yet been finally settled, but for the present we have adopted the terms recommended by the American Society of Biological Chemists,³ i e, the letter "B" to represent the antineuritic, and the letter "G" to indicate the antipellagic, factor.

Practically all of the literature on the pathologic changes resulting from vitamin B deficiency deals with the vitamin B complex,⁴ and a

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1 Smith and Hendrick. Pub Health Rep **41** 201, 1926. Goldberger, Wheeler, Lillie and Rogers. Ibid **41** 297, 1926. Goldberger and Lillie. Ibid **41** 1025, 1926. Chick and Roscoe. Biochem J **21** 698, 1927. Sherman and Anshwyer. J Biol Chem **75** 207, 1927. Hunt. Ibid **78** 83, 1928. Evans and Burr. Ibid **76** 263, 1928. Sure. Ibid **80** 297, 1928. Salmon, Hays, and Guerrant. Etiology of Dermatitis of Experimental Pellagra of Rats, J Infect Dis **43** 426, 1928. Sherman and Sandels. Proc Soc Exper Biol & Med **26** 536, 1929.

2 McCollum and Kennedy. J Biol Chem **24** 491, 1916.

3 Science **69** 276, 1929.

4 Jackson. The Effects of Inanition and Malnutrition on Growth and Structure, Arch Path **7** 1042, 1929, Ibid **8** 81 and 273, 1929.

large part of it is concerned with work on pigeons,⁵ hence, no attempt has been made to review any of this work. For a complete summary on the subject, the reader is referred to Jackson's recent review.⁴ The only article dealing somewhat with the gross and microscopic changes resulting from uncomplicated vitamin B deficiency that has come to our attention since the completion of our study is that of Findlay,⁶ but the greater part of his paper treats of the antipellagric factor, vitamin B₂, which is the tentative nomenclature adopted by the English biochemists for this dietary essential.

The stimulus for our investigation of tissue changes in avitaminosis was the discovery by Sure and Schilling several years ago that the nursing young of the albino rat, the maternal diet of which contained an insufficient amount of the vitamin B complex for lactation, died without hemorrhages in the osteogenic tissues, particularly at the juncture of the occipital and parietal bones.⁷ Therefore, the first study concerned itself with nursing young suffering from a deficiency of the vitamin B complex. In this connection we examined only the histologic changes in the liver. Later, the perfection of a biologic method for the production of uncomplicated vitamin B deficiency in nurslings of the albino rat⁸ enabled us to investigate the possible histologic effect of such avitaminosis. We then turned our attention to weaned and growing rats. In this communication, we summarize our observations on animals that have been deprived of the vitamin B complex and of vitamin B alone.

In previous publications, Sure, Kik and Walker, and Sure and Smith⁹ demonstrated that in vitamin B deficiency and in deficiency of the vitamin B complex anhydropenia develops, associated with a disturbance in hematopoietic function, although no definite anemia was established. This condition was encountered in nurslings, as well as in weaned animals. Sure and Smith¹⁰ found an increase in the nonsugar reducing substances in uncomplicated vitamin B deficiency. The most marked biochemical change noted was a reduction in the glycogen content of the liver.¹¹

The rations used and the results of the present investigation are summarized in tables 1 to 5 inclusive and in figure 1.

5 McCarrison. Indian Med Res Mem No 10, 1928, p 1. Sundararajan Ibid, p 59.

6 Findlay. J Path & Bact **31** 353, 1928.

7 Sure and Schilling. Vitamin Requirements of Nursing Young. II. The Production of Beriberi in the Nursing Young (*Mus Norvegicus Albinus*) Associated with Hemorrhages, Am J Dis Child **35** 811, 1928.

8 Sure and Smith. J Nutrition **1** 537, 1929.

9 Sure, Kik, and Walker. J Biol Chem **82** 287, 1929. Sure and Smith Ibid **82** 307, 1929.

10 Sure and Smith. J Biol Chem **84** 727, 1929.

11 Sure and Smith. Proc Soc Exper Biol & Med **27** 861, 1929.

TABLE 1—Composition of Rations

Components	Stock Diet 1*	Stock Diet 6*	Ration						
			1009†	1654	1145	1438	1432	1676	1646
Whole wheat	27 0	27 0							
Rolled oats	26 0	26 0							
Yellow corn	25 0	20 0							
Rice polishings		5 0							
Linseed oil meal	15 0	15 0							
Commercial casein	5 0	5 0							
Cod liver oil	1 0	1 0							
Sodium chloride	0 5	0 5							
Calcium carbonate	0 5	0 5							
Casein (purified)§			20	18	20	20	20	18	18
Agar agar			2						
McCullum's salts 185			4	4	4	4	4	4	4
Butter fat			5	10	5	5	5	10	8
Northwestern yeast					10				
Autoclaved yeast						10	5	5	5
Dextrin			69	68	61	61	66		
Cod liver oil									2
Corn starch								6	6

* These rations were supplemented with a liberal supply of cow's milk daily

† This ration was supplemented with 6 drops of cod liver oil daily to each animal

§ Purified by extraction for one week with water acidulated with acetic acid

TABLE 2—The Effect of Deficiency of the Vitamin B Complex and of Uncomplicated Vitamin B Deficiency on the Amount of Fat in the Livers of Nursing Young of the Albino Rat

Diet	Animals	Range in Ages, Days	Range in Weight, Gm	Percentage of Cases				
				++++	+++	++	+	None
Deficient in vitamin B complex	67	18 to 29	20 to 35	7 46	16 42	31 34	38 81	5 97
Deficient in vitamin B	80	26 to 41	17 to 30	0	0	0	16 30	83 70
Control stock diet 1	32	18 to 26	20 to 45	0	0	0	40 63	59 37
Control, stock diet 6	55	4 to 40	8 to 98	0	0	23 64	34 55	41 81
Control, high yeast diet (1145)	69	19 to 21	25 to 30	0	11 60	11 60	7 24	69 56

TABLE 3—The Effect of Age on the Weights of Liver and Spleen of Nursing Young and of the Weaned Young of the Albino Rat on Stock Diet 1

	Age, Days	Body Weight, Gm	Liver		Spleen	
			Weight, Gm	Percentage of Body Weight	Weight, Gm	Percentage of Body Weight
Nursing young of mothers on stock diet 1	4 (6)*	8 0	0 4676	5 84	0 0492	0 61
	8 (6)	14 4	0 6069	4 33	0 0788	0 56
	12 (5)	15 4	0 6282	4 08	0 0700	0 45
	15 (12)	23 2	0 8769	3 78		
	16 (12)	21 0	0 8615	4 12	0 0712†	0 38†
	19 (4)	30 0	1 4675	4 69	0 0845	0 28
	24 (5)	33 2	1 7293	5 20	0 1183	0 36
	28 (6)	47 5	3 3173	6 98	0 1930	0 41
Weaned young on stock diet 1	31 (6)	59	4 1203	6 98	0 2188	0 37
	36 (6)	75	5 6120	7 48	0 3232	0 43
	40 (8)	77	5 2304	6 79	0 2949	0 38

* Numbers in parentheses refer to numbers of animals taken for that particular age

† The figures for the spleen weights are the average of six nurslings

TABLE 4—*The Effect of Deficiency of the Vitamin B Complex and of Uncomplicated Vitamin B Deficiency on the Weights of Liver and Spleen of Nursing Young of the Albino Rat*

	Age, Days	Body Weight, Gm	Liver		Spleen	
			Weight, Gm	Percentage of Body Weight	Weight, Gm	Percentage of Body Weight
Deficiency of vitamin B complex	16 (6)*	12.0	0.4577	3.81		
	17 (5)	15.0	0.5848	3.90	0.0259	0.17
	19 (4)	21.0	1.4040	5.83	0.0538	0.22
	22 (6)	16.0	0.9291	5.70	0.0308	0.19
	24 (6)	20.0	1.4920	7.46		
	30 (6)	19.0	1.1172	6.40		
Uncomplicated vitamin B deficiency	26 (12)	24.5	1.1658	4.34	0.0666	0.27
	28 (6)	21.0	1.2196	5.80	0.0432	0.20
	33 (2)	23.0	1.4813	6.44	0.0370	0.16
	35 (6)	27.5	2.2647	8.23	0.0611	0.22
	41 (5)	24.0	1.6310	6.81		

* Numbers in parentheses refer to numbers of animals taken for that particular age

TABLE 5—*Comparison of Weights of Adrenal Glands, Spleen, Heart and Liver of the Weaned Albino Rat During a Period of Growth on Control Diets, with Those of the Albino Rat During a Period of Deficiency of the Vitamin B Complex and During a Period of Uncomplicated Deficiency of Vitamin B*

Diet	Age, Days	Animals	Body Wt., Gm	Adrenals		Spleen		Heart		Liver	
				Weight, Gm	Per Cent	Weight, Gm	Per Cent	Weight, Gm	Per Cent	Weight, Gm	Per Cent
Control diets ration 1452 plus from 30 to 150 mg. of an alcoholic extract from yeast foam daily	136	3	164	0.0263	0.016	0.6335	0.38	0.7139	0.43	6.81	4.15
	142	2	162	0.0259	0.016	0.3528	0.22	0.6707	0.41	6.85	4.22
	148	3	186	0.0223	0.012	0.4322	0.23	0.7245	0.39	7.57	4.07
Stock diet G	92	3	201	0.0185	0.009	0.9403	0.46	0.8441	0.45	8.6000	4.27
	97	4	194	0.0211	0.011	0.8873	0.46	0.8625	0.43	8.4914	4.34
	110	6	204	0.0254	0.012	0.7870	0.38	0.8504	0.41	9.4756	4.63
	118	7	196	0.0253	0.013	0.6358	0.33	0.8168	0.42	9.2800	4.73
Diet deficient in the vitamin B complex ration 1009	70	2	58	0.0196	0.033	0.1937	0.33	0.3680	0.63	2.6757	4.61
	71	1	47	0.0150	0.032	0.1252	0.27	0.3234	0.68	1.0580	2.23
	73	2	60	0.0269	0.045	0.1775	0.29	0.4609	0.76	2.4435	5.74
	76	2	57	0.0229	0.040	0.1575	0.21	0.4560	0.80	2.5411	4.45
	78	1	56	0.0261	0.046	0.1928	0.34	0.3254	0.58	2.4420	4.36
	87	2	60	0.0198	0.033	0.1253	0.21	0.5105	0.85	4.4405	7.34
	89	2	67	0.0134	0.020	0.1319	0.19	0.4828	0.72	3.1057	4.63
	95	3	67	0.0136	0.020	0.1787	0.26	0.4254	0.63	3.0487	4.55
Uncomplicated vitamin B deficiency ration 1452 supplemented daily with from 5 to 10 mg. of vita- min B con- centrate S2	78	7	64	0.0174	0.027	0.1726	0.27	0.4279	0.68	3.0190	4.72
	82	5	76	0.0161	0.021	0.1738	0.23	0.5076	0.67	3.2372	4.26
	94	2	62	0.0232	0.037	0.1610	0.26	0.3612	0.58	3.7129	5.98
	99	1	53	0.0218	0.041	0.2155	0.41	0.4016	0.76	3.5949	6.78
	122	1	88	0.0272	0.031	0.1967	0.22	0.3989	0.45	5.9400	6.75
	127	1	88	0.0186	0.021	0.1649	0.19	0.5906	0.67	4.6400	5.27
	134	1	74	0.0210	0.029	0.1760	0.24	0.5380	0.73	3.6850	4.94
	142	2	108	0.0315	0.029	0.2955	0.27	0.5145	0.47	4.5277	4.19

PATHOLOGIC CHANGES IN NURSING YOUNG OF THE ALBINO RAT

Deficiency of the Vitamin B Complex—Deficiency of the vitamin B complex was produced in the nursing young of the albino rat by a method previously developed by one of us (B S¹²), using ration 1009¹³ supplemented with enough of the vitamin B complex for maternal welfare, but not for lactation. On such a dietary, nurslings manifested first a cessation of growth, followed by posterior paralysis, which later, unless vitamin therapy was readily instituted, became general, so that it extended to the center of deglutition. Frequently the young developed spasms accompanied by shrills and running fits. They became so tense as to bite the screens of the cage so that they bled from the mouth. It was a rather surprising coincidence that the mothers

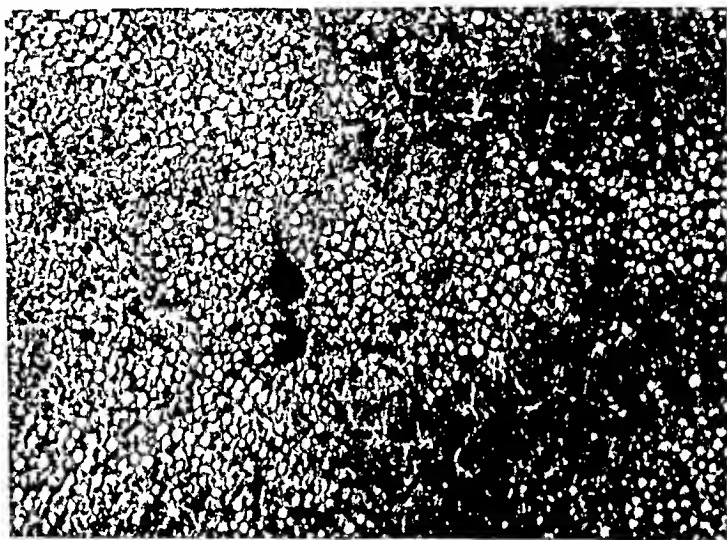


Fig. 1—Photomicrograph of liver of a nursing of an albino rat suffering from a deficiency of the vitamin B complex. It shows marked vacuolation indicating fatty metamorphosis around the central vein. The weight of the young rat was 29 Gm. and its age 27 days.

stored vitamin in the tissues on the dietary referred to when the young were dying or struggling for independence. Since the young were found dying with their stomachs full of curdled milk, the conclusion drawn was that the derangement must be associated with poor quality rather than with insufficient quantity of milk.⁷ In addition to hemorrhages of bones, the most noteworthy observation that we made in this investigation was that such nurslings showed marked fatty metamorphosis of the liver. This is illustrated in figure 1. For this study we employed sixty-seven young rats, from 18 to 29 days of age, and

¹² Sure, J. Biol. Chem. **76**, 685, 1928.

¹³ The composition of this ration, as well as those of other rations is given in table 1.

ranging in weight from 20 to 35 Gm. Some of the tissues were preserved in formaldehyde and stained with eosin and Delafield's hematoxylin or eosin and iron hematoxylin. Numerous sections were frozen and stained with sudan III. Comparisons were made with groups fed three different types of control diets. It is apparent from table 2 that, although on control stock diet 6 and on control diet 1145 an appreciable amount of deposit of fat in livers was observed, the ration deficient in the vitamin B complex produced the most marked fat deposits. Since the majority of the nurslings suffering from deficiency of vitamin B complex (table 4) compared with controls (table 3) had an increase in the weight of the liver in proportion to the body weight, the marked vacuolation observed around the central vein (fig. 1) and also in the periphery of the hepatic lobule is indicative of fatty infiltration. An analysis of tables 3 and 4 also discloses that nurslings deprived of optimum amounts of the vitamin B complex had atrophy of the spleen.

Uncomplicated Vitamin B Deficiency—For this investigation eighty nurslings were used. The uncomplicated avitaminosis was produced in nursing young of the albino rat on maternal diet 1145, supplying an adequacy of vitamin G, but an inadequacy of vitamin B.¹⁴ Employing such biologic technic, we first encountered prolonged maintenance of the nursing young. Eventually they presented posterior paralysis, labored respiration and cyanosis, and finally, unless vitamin B therapy was instituted, death ensued.

Previous work had demonstrated that in young rats suffering from this avitaminosis, hypoglycemia and anhydremia associated with hematopoietic disturbance develop.¹⁴

Such young had no noteworthy fatty changes in the liver, although there was an increase in the weight of the liver (calculated as percentage of body weight) (table 4) compared with young on the control diets (table 3). Such young, however, had atrophy of the spleen. The most pronounced biochemical change noted in nurslings suffering from uncomplicated vitamin B deficiency was the marked reduction in the glycogen content of the liver. In twenty-nine control animals, the liver glycogen expressed in milligrams of dextrose per hundred grams of liver was from 7.02 to 14.98, while in the vitamin B deficient animals the range of this constituent was from 0.12 to 2.53 mg.¹⁵ No noteworthy changes were found in the rest of the tissues, with the exception of, in a few animals, interstitial pancreatitis and ulcers of the stomach.

¹⁴ Sure and Smith (footnote 9)

¹⁵ These observations were made by Margaret Elizabeth Smith of the Department of Home Economics

PATHOLOGIC CHANGES IN THE WEANED ALBINO RAT

Deficiency of the Vitamin B Complex—For this study, we employed fifteen animals. The deficiency was produced by feeding rations 1009 and 1654. Comparisons were made with twenty-eight animals fed two types of control diets, 1 and 6 (table 1). The period of observation ranged from thirty-five to fifty-seven days, during which there occurred a loss of weight in each animal of from 12 to 29 Gm. The main pathologic changes observed were those associated with inanition, with the exception of hypertrophy of the adrenal glands and the heart (table 5), and fatty metamorphosis of the liver in some animals without the accompanying increase in the weight of the liver. Since all the organs were weighed quickly to prevent evaporation, the hearts were weighed with considerable amounts of blood, and it is possible that the increased weights of the hearts of animals deprived of the vitamin B complex were due to the increased blood flow through that organ, as found by Simonds and Brandes¹⁶ in experimental hyperthyroidism in the dog. At least, our observations on the hypertrophy of the adrenal glands and heart of the albino rat suffering from a deficiency of the vitamin B complex are in agreement with the recent observations of McCarrison and that of Sundarajan in beriberi columbarum.⁵

Uncomplicated Vitamin B Deficiency—In the early part of 1926 Smith and Hendrick¹ demonstrated the dual nature of the vitamin B complex. They reported that rolled oats is not deficient in vitamin B but in another factor which is present in brewer's yeast, and which withstands autoclaving for six hours at 15 pounds (6.8 Kg.) of pressure. Simultaneously with the publication of the work of Smith and Hendrick appeared the paper of Goldberger, Wheeler, Lillie and Rogers¹ in which they established the existence of two vitamins associated with the vitamin B complex. The results of the latter investigators have been since confirmed by Chick and Roscoe,¹ Salmon, Hays and Gueriant,¹ Sherman and Axtmayer¹ and others. The procedure of furnishing the stable antipellagric factor, vitamin G, has now been generally adopted by the introduction of autoclaved yeast. For our work, we used as a source of vitamin G a baker's dried yeast secured from the Northwestern Yeast Company, Chicago, which we autoclaved for six hours in shallow glass pyrex dishes, about 75 mm. deep, at from 15 to 18 pounds (6.8 to 8.2 Kg.) pressure.

Uncomplicated vitamin B deficiency was produced in fourteen weaned albino rats by feeding ration 1676. The period of observation ranged between 39 and 66 days, during which the average loss of weight was 22 Gm. Since on this ration, in the majority of animals, loss of weight

¹⁶ Simonds and Brandes. The Effect of Experimental Hyperthyroidism and of Inanition on the Heart, Liver and Kidneys, Arch. Path. 9:445, 1930.

was encountered as early as the second week, accompanied by inanition, an attempt was made to prolong the period of vitamin B deficiency by furnishing daily small amounts of a vitamin B extract used previously in our work⁸ which would facilitate the production of prolonged maintenance, and thus circumvent the associated phenomenon of starvation. Similar cases accompanied by small gains of body weight due to an inadequate supply of vitamin B were encountered in animals fed ration 1452 fortified with daily amounts of from 5 to 10 mg. of our vitamin B concentrate⁸². On the latter dietary regimen we employed fifteen animals, the experimental period lasting for from 61 to 121 days. The average gain in weight of each animal was 12.6 Gm. during an average period of 86 days.

An examination of the results in rats fed a ration deficient in vitamin B, compared with the results in control animals (table 5) indicates that in uncomplicated vitamin B deficiency the adrenal glands weighed considerably more in proportion to the rest of the body weight. This was also true of the heart. In the heart, however, we determined that the increase in weight was due mainly to additional volumes of blood. These results, it will be noted, were observed in animals the condition of which was uncomplicated by the phenomenon of starvation, since they were on ration 1452 supplemented with small amounts of a vitamin B extract, which allowed even small gains in weight.

The gross pathologic changes observed in the animals on ration 1676, in which loss of weight was produced, accompanied by inanition, were emaciation, marked dilatation of the stomach with undigested food, hypertrophy of the adrenal glands and heart and atrophy of the spleen.

Microscopic Changes in Uncomplicated Vitamin B Deficiency The heart, stained with sudan IV, revealed no fat, except that normally present in the pericardium.

The spleen showed atrophy, as diagnosed by decrease in parenchymal structures with connective tissue replacement. Hemosiderin was present to a great extent.

The gastro-intestinal tract was normal, except for a small ulcer in one stomach. Our histologic observations on the gastro-intestinal tract were essentially in agreement with those of Findlay. This investigator studied, in addition, mitochondria of the cells of the stomach and intestines. He reported that "in the chief cells of the stomach and in the cells of the glands of Lieberkuhn there was some transformation of the rod-like mitochondria into granules"⁶.

No study was made of the peripheral nervous system.

The liver presented no apparent change, except a slight amount of fatty changes irregularly distributed in fine droplets, in one animal. Three sections indicated focal necrosis.

The thymus showed atrophy, as indicated by connective tissue replacement

No noteworthy histologic changes were present in the lungs, aorta, kidneys, salivary glands, thyroid gland, tongue or pancreas

VITAMIN B, GROWTH AND FOOD INTAKE

It has been generally assumed that beneficial effects of vitamin B on growth and general well-being result indirectly through increase of food consumption, since the administration of vitamin B, which is generally given in liberal amounts, is always accompanied by an increase of appetite. During the last two years we had occasion to test in the laboratory vitamin B concentrates prepared by one of us (B. S.) by the Sherman method of biologic assay¹⁷. This method consists in feeding daily to weaned litter mates (experimental rats) graduated amounts of materials containing vitamin B as a supplement to, and separately from, a diet satisfactory except for vitamin B, an average gain of approximately 3 Gm per week per rat for a period of eight weeks was noted. One of the vitamin B concentrates recently developed for human application is so potent that 0.7 mg daily produces this desired amount of growth. This vitamin B extract we have designated as concentrate 89. Two animals of the same litter, which received the basal ration without any supplement of vitamin B (the negative controls) consumed as much food as two comparable litter mates receiving the vitamin extract but the different results in growth were striking. For instance, ♀ 6597 negative control, ate 139 Gm during the experimental period and lost 21 Gm, ♀ 6593, which received a daily supplement of from 0.4 to 0.7 mg of vitamin B concentrate 89, and consumed 140 Gm, gained 14 Gm. Also, ♀ 6596, which received a daily supplement of from 0.4 to 0.9 mg of the same vitamin extract and ate 137 Gm, lost 11 Gm less than the control litter mate, ♀ 6597, on comparable food intake. The second control, ♂ 6598, ate 224 Gm and gained 2 Gm while ♂ 6594 the litter mate on comparable food consumption (228 Gm) with vitamin B supplement, gained 18 Gm, while the last litter mate, ♂ 6595 with a food intake of even 18 Gm less (210 Gm) than the litter mate control, gained 46 Gm. These results, obtained in animals receiving small amounts of vitamin B supplements for slow growth, conclusively demonstrate the specific effect of vitamin B per se on growth, unrelated to food intake.

¹⁷ Sherman Food and Nutrition, New York, The Macmillan Company, ed. 3, 1927, p. 308.

THE EFFECT OF UNCOMPLICATED VITAMIN B DEFICIENCY ON THE
TOTAL AND DIFFERENTIAL LEUKOCYTE COUNT

In 1921, Cramer, Drew and Mottram¹⁸ reported that a diet deficient in vitamin B resulted in atrophy of lymphoid tissue throughout the body and in lymphopenia in the circulating blood of mice and rats. In 1922, Happ¹⁹ observed leukopenia in the rat suffering from vitamin B deficiency. Recently, Sure, Kik and Walker²⁰ could find no appreciable change in the total leukocyte count in albino rats on a dietary deficient in the vitamin B complex.

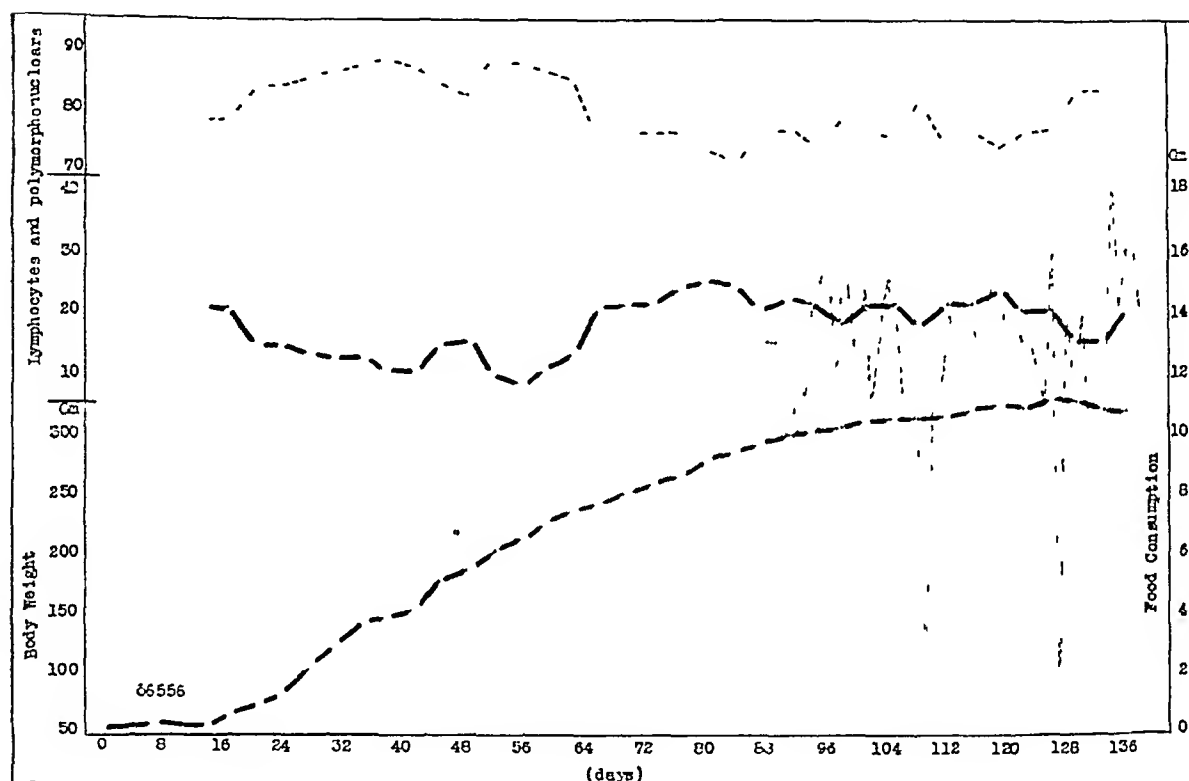


Fig 2—Total lymphocyte and polymorphonuclear counts on ration 1202. The upper curve in dotted lines represents total lymphocytes in per cent, the middle curve in heavy lines, total polymorphonuclear leukocytes in per cent, the lower curve in dotted lines, food consumption in grams, and the lower curve in heavy lines, body weight in grams.

In this investigation, a study was made of the total and differential count in eighteen albino rats suffering from uncomplicated vitamin B deficiency. The avitaminosis was produced on a dietary described in the second paper of this series.²¹ The animals were taken in groups of six,

18 Cramer, Drew, and Mottram. *Lancet* **1** 963, 1921, *ibid* **2** 1202, 1921, *Proc Roy Soc London* **93** 449, 1922.

19 Happ. *Bull Johns Hopkins Hosp* **33** 163, 1923.

20 Sure, Kik, and Walker. *J Biol Chem* **83** 387, 1929.

21 Thatcher, Sure, and Walker. *Avitaminosis. II. Pathologic Changes in the Albino Rat Suffering from Vitamin G Deficiency*, *Arch Path*, this issue, p 425.

which were litter mates, the fifth and sixth animals were controls, which were given our ration 1202 containing 5 per cent of unactivated dehydrated baker's yeast as a source of vitamins B and G. The total leukocyte and differential counts were made twice weekly, peripheral blood from the tail being used according to the technic of Hart and his co-workers²². Wright's stain was used for the differential count. No attempt was made to distinguish the small from the large lymphocytes, both being included under the total lymphocyte count. Typical illustrations of our results are presented in figures 2 and 3. No noteworthy change in the total leukocyte count was found in this avitaminosis

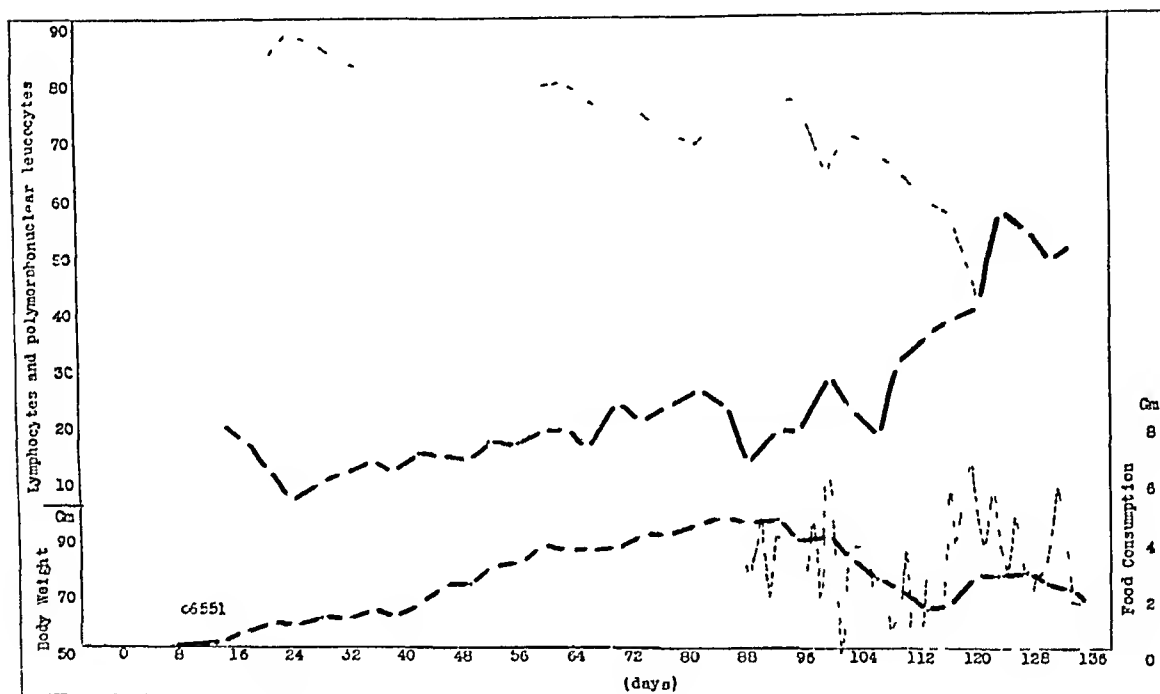


Fig 3—The effect of vitamin B deficiency on the total lymphocyte and polymorphonuclear leukocyte counts. The upper curve in dotted lines represents total lymphocytes in per cent, the middle curve in heavy lines, total polymorphonuclear leukocytes in per cent, the lower curve in dotted lines, food consumption in grams and the lower curve in heavy lines, body weight in grams

There was, however, a pronounced effect on the polymorphonuclear-lymphocyte ratio, the lymphocytes being markedly reduced, with a corresponding increase in the polymorphonuclears. In the control animals, age and increase of body weight did not produce any appreciable change in the distribution of either the polymorphonuclears or the lymphocytes. Uncomplicated vitamin B deficiency produced no effect on the monocytes, eosinophils or basophils.

²² Hart, Steenbock, Elvehjem, and Waddell. *J Biol Chem* 65: 67, 1925

Since in vitamin B deficiency the phenomenon of anorexia is always encountered, the question arises: Is the disturbance in the polymorphonuclear-lymphocyte ratio an expression of inanition? It is apparent however, from the illustration given in figure 3 that, while there is a considerable reduction in food intake, the lymphopenia and corresponding polymorphonuclear leukocytosis are observed during periods when there is an intake of appreciable amounts of food. At least, the disturbance in the differential count is not due to starvation: a lack of an optimum food intake may, however, be a contributing factor.

SUMMARY

Nursing young of the albino rat suffering from a deficiency of the vitamin B complex show fatty metamorphosis of the liver. Such young also have atrophy of the spleen, as well as hemorrhages in osteogenic tissues and anhyemia associated with disturbance in hematopoietic function.

Nursing young of the albino rat suffering from uncomplicated vitamin B deficiency have marked reduction in the glycogen content of the liver and atrophy of the spleen, as well as hypoglycemia and anhyemia associated with hematopoietic disturbance.

The pathologic changes observed in weaned albino rats deprived of the vitamin B complex are mainly those associated with inanition. In addition, hypertrophy of the adrenal glands and of the heart has been noted. Fatty metamorphosis of the liver has also been observed in some animals.

Observations on weaned albino rats suffering from uncomplicated vitamin B deficiency have been made on two groups of animals: (1) those entirely deprived of vitamin B and (2) those securing daily amounts of vitamin B inadequate for optimum growth and welfare. Atrophy of the spleen and hypertrophy of the adrenal glands and heart (in the latter organ mainly due to increased blood volume) were the changes noted, but the significance of these observations is that they were noted on animals of group 2 that showed even a slight gain in body weight and, therefore, were uncomplicated by inanition.

Vitamin B *per se* possesses the function of producing growth unrelated to food intake.

Uncomplicated vitamin B deficiency in the albino rat produces lymphopenia and a corresponding polymorphonuclear leukocytosis.

AVITAMINOSIS

II PATHOLOGIC CHANGES IN THE ALBINO RAT SUFFERING FROM VITAMIN G DEFICIENCY *

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In February, 1926, Goldberger, Wheeler, Lillie and Rogers¹ demonstrated the dual nature of the dietary essential, vitamin B. The differentiation was made mainly on the basis of thermostability. In May, 1926, Goldberger and Lillie² produced evidence that a deficiency of the stable factor in a diet fortified with an abundance of the labile, antineuritic vitamin resulted in a pellagra-like disease in the rat. Following the arrest of growth, alopecia, bilateral symmetrical lesions of the skin, stomatitis and ophthalmia were noted. The conclusion the authors made was that it is probable that the pellagra-like condition in the rat may be the analogue of pellagra in man, but that additional evidence is necessary to establish this fact. It may be pointed out that this is the first time since 1913-1914, when McCollum and Davis³ and Osborne and Mendel⁴ described a lesion of the eye in vitamin A deficiency, that ophthalmia has been found associated with a dietary deficiency, and that it would therefore be erroneous in the future to designate vitamin A as the antiophthalmic vitamin, as has been done in the past. The "saltophthalmia" reported in 1922 by McCollum, Simmonds and Becker⁵ was later found by Simmonds, Becker and McCollum⁶ to be due to a deficiency in vitamin A rather than to a mineral deficiency.

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1 Goldberger, Wheeler, Lillie, and Rogers. Pub Health Rep **41** 297, 1926

2 Goldberger and Lillie. Pub Health Rep **41** 1025, 1926

3 McCollum and Davis. J Biol Chem **15** 167, 1913, *ibid* **19** 245, 1914

4 Osborne and Mendel. J Biol Chem **16** 423, 1913-1914

5 McCollum, Simmonds, and Becker. J Biol Chem **53** 313, 1922, *ibid* **64** 161, 1925

6 Simmonds, Becker, and McCollum. J Nutrition **1** 39, 1929

In 1927, Chick and Roscoe⁷ corroborated the main observations of Goldberger and Lillie,² designating the stable factor as B₂ according to the English nomenclature. They suggested that they might be dealing with more than one dietary deficiency, for animals occasionally deprived of B₂ remained stunted in growth, but exhibited no special lesions of the skin.

In 1928, Salmon, Guérant and Hays⁸ confirmed the work of Goldberger and Lillie, but in addition reported the presence of a gram-positive coccus, which they obtained from skin and arthritic lesions, parenchymatous organs and the walls of the intestines.

Recently Chick and Roscoe⁹ demonstrated that the so-called antipellagric factor is unstable at temperatures of from 122 to 125 C in an alkaline medium.

In March, 1929, Sherman and Sandels¹⁰ described their experiences with vitamin G deficiency in the albino rat. Their observations were similar to those reported by Goldberger and Lillie² and by Chick and Roscoe⁹.

After the completion of our investigation, the results of which are submitted in this communication and a preliminary report of which appeared recently,¹¹ the work of Findlay¹² published in 1928 came to our attention. Our observations conform to a great extent to his, further reference to which will be made later in the paper.

RATIONS EMPLOYED

Table 1 gives the composition of the rations employed in this study. Ration 1522 is a duplicate of the one reported by Hunt,¹³ abundant in vitamin B, but extremely deficient in vitamin G (according to this investigator) from the standpoint of growth. Ration 1521 is a duplicate of ration 1522 slightly modified to reduce the salt content from 5 to 4 per cent. In an effort to construct satisfactory diets for the development of vitamin G deficiency, it was anticipated that our method of freeing casein from the vitamin B complex, which consists in extraction for one week with acidulated water, might be inadequate for the complete removal of the stable factor. In a number of experiments we therefore used casein that had been extracted with 60 per cent alcohol according to the method of Sherman and Spohn¹⁴ subsequent to extraction with acidulated water (ration 1654-b). The method of preparation of the vitamin B supplement furnished by

7 Chick and Roscoe. *Biochem J* **21** 698, 1927, *ibid* **22** 790, 1928.

8 Salmon, Guérant, and Hays. *Etiology of Dermatitis of Experimental Pellagra in Rats*, *J Infect Dis* **43** 426, 1928.

9 Chick and Roscoe. *Biochem J* **24** 105, 1930.

10 Sherman and Sandels. *Proc Soc Exptl Biol & Med* **26** 536, 1929.

11 Thatcher, Sure, and Walker. *South M J* **23** 143, 1930.

12 Findlay. *J Path & Bact* **31** 353, 1928.

13 Hunt. *J Biol Chem* **78** 83, 1928.

14 Sherman and Spohn. *J Am Chem Soc* **45** 2719, 1923.

an alcoholic extract from dried baker's yeast was that described by Sherman and Sandels¹⁰ In ration 1654-c we used casein that had been irradiated for ten hours with a mercury quartz vapor lamp (after extraction with acidulated water), following the suggestion of Hogan and Hunter¹⁵ that such treatment destroys vitamin G, but leaves vitamin B intact The latter idea was also introduced in the development of the following dietary, which was found the optimum (from the months of April to September, 1929) for the production of vitamin G deficiency accompanied by dermatitis Rations 1640 and 1692 were supplemented as described in table 1 with from 300 to 500 mg of rice polishings that had been irradiated for ten hours with a mercury quartz vapor lamp, as a source of vitamin B Irradiating the casein of the rations seemed to expedite the onset of dermatitis in those animals in which the skin lesions developed Ration 1641 is our ration 1009¹⁶ deficient in the vitamin B complex and supplemented with from 30 to 60 mg daily of vitamin B concentrate 82 (used previously in studies on the biochemistry of avitaminosis,¹⁷ which furnishes an abundance of vitamin B, but an inadequate amount of vitamin G, for optimum growth and welfare

TABLE 1—Composition of Rations

Dietary Components	Ration							
	1521	1522	1640†	1641‡	1692#	1654 a	1654 b	1654 c
Casein*	20	18	20	20	18			18
Casein¶						18		
Casein§							18	
Corn meal	25	25						
McCollum's salts no 185	4	5	4	4	4	4	4	4
Cod liver oil	2	2						
Butter fat			5	5	10	10	10	10
Crisco	10	10						
Starch	39	40						
Agar agar			2	2				
Dextrin			69	69	68	68	68	68

* Purified by extraction for one week with water acidulated with acetic acid

¶ Purified by extraction with 60 per cent alcohol

§ Irradiated for ten hours with a mercury quartz vapor lamp

† This ration was supplemented as follows: six drops of cod liver oil was administered to each animal daily, 100 mg of an alcoholic extract from yeast was given for from forty to fifty days until growth ceased, then the administration of this preparation was replaced by that of 500 mg of rice polishings, irradiated for ten hours, daily to each animal, as a source of vitamin B

‡ This ration was supplemented by the administration of 6 drops of cod liver oil and from 30 to 60 mg of vitamin B concentrate 82 (an extract from rice polishings) daily to each animal

On the twenty first day after the initiation of the experiment, the ration was supplemented with from 300 to 500 mg of rice polishings, irradiated for ten hours with a mercury quartz vapor lamp

|| After the animals had depleted their reserves of the vitamin B complex, this ration was supplemented with from 100 to 200 mg daily of an alcoholic extract from baker's yeast

GENERAL OBSERVATIONS

A summary of our observations on the symptomatology of vitamin G deficiency is presented in table 2 Sixty-four animals were studied on the different vitamin G-deficient rations Comparisons were made with twelve animals on ration 1,452 (table 1) containing autoclaved

15 Hogan and Hunter J Biol Chem 78 433, 1928

16 Sure J Biol Chem 76 673, 1928

17 Sure and Smith J Nutrition 1 537, 1929

TABLE 2—*Pathologic Symptoms Observed in the Albino Rat on Rations Deficient in Vitamin G*

Ration	Animal	Duration of Experiment, Days	Change of Weight During Experiment, Gm	Period After Which Growth Ceased, Days	Dermatitis, Period of Onset, Days	Ophthalmia, Period of Onset, Days	Chromogenic, Urine, Period of Onset, Days	Incontinence of Urine, Period of Onset, Days
1521	♀ 6136	140	+17	84				
	♀ 6137	140	+26	69	120	34	72	34
	♂ 6138*	140	+55	115	106†			
	♂ 6139	140	+35	84				
	♂ 6140*	140	+20	86	83	80		
	♂ 6141*	87	+1	86		54	41	
1522	♀ 6142	133	+29	69				
	♀ 6143#	121	+24	69				
	♀ 6144	92	+22	46				
	♂ 6145	92	+12	50			75	75
	♂ 6146	127	+35	62	89			
	♂ 6147*	45	+20	58	61			
1640	♂ 5952	189	+85	146	87¶		42¶	
	♀ 5953	98	+22	83	28¶	33¶	36¶	36¶
	♀ 5960	132	+20	96	48¶			
	♂ 5961	139	+0	96	48¶			
	♀ 5962	117	+49	94	77¶			
	♀ 5963	131	+16	108	66¶	25¶	15¶	
1692	♀ 6124	104	+42	98				
	♀ 6125	104	+74	98				
	♀ 6126	147	+102	146	93¶			
	♂ 6127‡	121	+6	86	34¶		34¶	
	♂ 6128	147	+65	99	80¶		50¶	
	♂ 6129	147	+71	146			50¶	
1641	♀ 5974	147	+117	147				
	♀ 5975	147	+67	139				
	♀ 5976	91	+60	83	52	56		
	♂ 5958	132	+31	109	127		114	127
	♂ 5959	147	+81	108				
	♀ 5964	147	+61	105				
	♀ 5965	76	+18	48				
	♂ 5966	153	+31	108	107	151	91	91
	♂ 5967	76	+4	69		76	75	75
	♂ 5969	77	+56	94	70			
1654 a	♀ 6016	132	+85	110				
	♀ 6017	62	+9	1				
	♀ 6018	175	+11	88	131	171		
	♂ 6019	143	+6	77	131		82	124
	♂ 6020	62	+4	14				
	♂ 6021	62	+1	14				
1654 b	♀ 6024	62	+5	1				
	♂ 6025	62	+11	1				
	♂ 6026	71	+6	1				
	♂ 6027	97	+4	75				
	♀ 6022§	42	+1	9				
	♂ 6023	61	+11	1				
1654 c	♀ 6028	65	+17	7				
	♀ 6029	65	+11	1				
	♂ 6030	114	+40	108	102			
	♂ 6031	114	+42	111	84		86	
	♀ 6032	62	+3	11				
	♀ 6033	62	+11	1				
	♂ 6080**	114	+6	90	98			
	♀ 6081**	122	+35	122				
1641	♀ 6078	70	+6	70				
	♀ 6079	70	+3	71				
	♀ 6082	70	+30	70	29		61	61
	♂ 6083	71	+3	51	29		61	61
1654 b††	♂ 6084	70	+6	63	62			
	♂ 6085	70	+8	16	62			
	♂ 6086	70	+11	1				
	♀ 6087	70	+7	1		70		
	♂ 6088	119	+32	91				
	♀ 6089	119	+44	114				

♀ indicates female ♂, male

* This rat's ration was supplemented from the twenty seventh day on with 100 mg daily of an alcoholic extract from rice polishings, irradiated for ten hours

† Slight eschars on left upper jaw

|| Animal was in dying condition twelve days before termination of experiment, responded to vitamin B therapy

Died, paralyzed on the previous day

¶ This period is calculated from the time the ration received the first supplement of irradiated rice polishings as a source of vitamin B

‡ Animal died before autopsy could be made

§ Animal died on forty second day

** Changed to ration 1654 b on eighty first day of experiment

†† Starch of ration replaced with dextran

yeast supplying vitamin G and supplemented with larger dosages of vitamin B concentrates, so that excellent growth was obtained without the accompaniment of any external pathologic changes. Comparisons were also made with twenty animals that showed excellent growth and all the external signs of normality on our stock diet 6 (table 1 in paper 1).

Dermatitis was encountered in twenty-seven of the sixty-four animals examined, or in 42 per cent. The incidence of ophthalmia, however, was only 15 per cent. Ophthalmia sometimes appeared before and sometimes after the dermatitis. It is also apparent from what has already been presented that dermatitis developed, unaccompanied by ophthalmia, in seventeen animals. Such results, as well as our failure to find stomatitis, seem to be contrary to the experience of previous investigators. Chlorogenic urine was found in 25 per cent and incontinence of urine in



Fig 1—Fresh lesions on the head of an albino rat suffering from vitamin G deficiency

14 per cent, of the animals studied. Pruritus was observed in seven, and diarrhea in only two, of the sixty-four animals, therefore, these symptoms are not associated specifically with vitamin G deficiency.

In the construction of the rations, one of the main objectives was to obtain evidence of a correlation between loss of weight and dermatitis. This information is essential if it is to be accepted that vitamin G is an antidermatitic factor and at the same time a growth-promoting dietary essential. Our results, shown in detail in table 2, evidence no such correlation. In fifteen of twenty-seven cases, the dermatitis preceded cessation of growth, while in over 50 per cent of the animals cessation of growth was not accompanied by any lesions of the skin. Such evidence does not justify the conclusion that the antidermatitic and growth-promoting syndromes associated with vitamin G deficiency are identical.

With the exception of the failure of continuous growth and the loss of body weight, dermatitis was the symptom most frequently

observed, 42 per cent of the animals presenting it. The following observations were made on the occurrence of dermatitis. The hair became thin and roughened. In these regions of alopecia, eschars with raised irregular edges appeared suddenly. The eschars averaged from 1 to 4 mm in their largest dimension. They were brownish red when the bleeding stopped, but later were gray, rough and irregular. When they were removed, there remained a moist, depressed surface. The lesions had a tendency to be bilateral, and they were present mainly on the side and top of the head (fig. 1) on the forepaws, shoulders and



Fig. 2—Marked hyperkeratosis in the skin of an albino rat suffering from vitamin G deficiency

jaws and around the eyes. Scratching caused some of the lesions, but we are not certain that it was the cause of all of them.

OBSERVATIONS AT AUTOPSY

The animals were killed with ether anesthesia, and complete autopsies were made immediately. Tissues were fixed in Zenker's solution without acetic acid and stained by the Giemsa method. Fixation with solution of formaldehyde and hematoxylin-eosin staining were also used. A general study of the important lesions was made.

Skin—Ulceration was the usual change. These ulcers varied in size and consisted of a varying amount of disintegrated tissue containing

polymorphonuclear leukocytes undergoing degeneration. The deeper layers of the skin were sometimes involved, and the granuloma might extend far into the musculature. Cells of the lymphocyte series were occasionally present. When the epidermis had disappeared, it was replaced by necrotic material. Hyperkeratosis was present on the sides of the ulcer and also in places in which the epidermis had not disappeared. It was sometimes present with no relation to the ulcer (fig. 2). Parakeratosis also occurred. Desquamation of keratinized material was frequent. Disintegration of the hair follicles, sebaceous glands and elastic fibers was prominent.

Gastro-Intestinal Tract—In several sections of the stomach, eosinophil polymorphonuclear leukocytes and a few cells of the lymphocyte series were more prominent between the glands and in the submucosa of the rumen than in the normal stomach. In one section of the rumen there was an ulcer, in another, there was a small abscess. Congestion of the intestines was almost constant. Hemorrhage was present in the villi to a great extent in the two animals in which hemorrhage was demonstrated grossly. Erosion of the epithelium occurred in the intestines to a slightly greater extent than in the control animals.

No papillomatous proliferation of the squamous epithelium occurred in the stomachs as reported by Findlay,¹² since our animals were on screens, and therefore had no opportunity to scatter hair that was shed.¹⁸

Liver—Several sections contained fat (sudan IV). This fat was in huge droplets, usually with a tendency to be arranged around the central vein. On our control diets,¹⁹ the liver of the albino rat represented 4.43 per cent of the body weight. On the rations deficient in vitamin G, the liver represented 6.39 per cent of the body weight.²⁰ Such results would indicate fatty infiltration.

Heart—Numerous sections of the heart muscle contained no fat in fibers (sudan IV). The weights of hearts of the animals showing vitamin G deficiency, compared with controls,²¹ indicated cardiac hypertrophy. This, however, as in the case of vitamin B deficiency, may have been due to the increased blood flow in that organ.

Spleen—Atrophy of the spleen was noted by decrease in parenchymal cells, increase in fibrous tissue and decrease in weight of the

18 Pappenheimer and Larimore. J. Exper. Med. **40**: 719, 1924.

19 For composition of diets see table 1 in Sure, Thatcher, and Walker. Avitaminosis. I. Pathologic Changes in Nursing and in Weaned Albino Rats Suffering from Vitamin D Deficiency, Arch. Path., this issue, p. 413.

20 These figures represent averages of all the animals under observation.

21 See table 5 of paper I (footnote 19).

organ The malpighian bodies had almost entirely disappeared, and there was replacement by connective tissue

Adrenal Glands—An increase in the weight of the adrenals was found, when calculated as percentage of the total body weight

Thymus—From the sections examined there was involution because of the presence of fat and fibrous tissue

Testicles—Active spermatogenesis was present

Other Observations—There were no noteworthy microscopic changes in the brain, thyroid gland, tongue, esophagus, kidneys, skeletal muscle, aorta, salivary glands, pancreas, lungs, ovaries or urinary bladder

COMPARISON OF OBSERVATIONS WITH THOSE MADE IN HUMAN PELLAGRA

The most puzzling point is that, although nine of twelve animals presented dermatitis on rations 1640 and 1692 which were deficient in vitamin G (table 1) during the period from April to September, 1929, only one of eighteen animals presented dermatitis on the same diets from September, 1929, to May, 1930. The other symptoms of vitamin G deficiency mentioned previously were, however, apparent in the warmer, as well as in the colder, months. Such observations seem to be in harmony with experience in human pellagra. Such results have been noted for the first time in the experimental production of vitamin G deficiency in the albino rat. At this writing, we are producing dermatitis successfully on the dietary referred to. As this is an important observation, because of its significance in the symptomatology of human pellagra, more data are being accumulated. MacNeil²² stated in his article on pellagra "that during the stage of progressive erythema the skin is very sensitive to external irritants, such as sunlight or even contact with the air." Our experimental rats were not exposed to direct sunlight, but they were in a room with an average afternoon temperature of 83 F.

Diarrhea was not a prominent symptom, as it is in many pellagrins. Constipation was also not present. Salivation did not occur as reported by Sherman and Sandels,¹⁰ but this is not important in pellagra. Stomatitis, one of the main symptoms reported by previous investigators, was not present in our rats. Loss of weight was common, and anorexia occurred in some animals in the terminal stages of the avitaminosis. These are frequent symptoms in human pellagra. The presence of ophthalmia and the lack of involvement of the nervous system could not be correlated with the human disease.

22 MacNeil. Am J M Sc 161 469 1921

Findlay¹² found dermatitis preceding alopecia, vesicles, swollen collagen fibers, atrophy of elastic tissue and congestion of the small blood vessels in the cutis, atrophy of the testicles, and certain lesions of the tongue and the stomach. We were unable to confirm the occurrence of these changes.

The lesions that we observed in the skin were not absolutely comparable with those found in man. Hyperkeratosis and parakeratosis with ulceration occurred, which might have eclipsed the early picture. However, the lesions were bilateral. Rarefaction of the superficial corium, as well as the fibrolytic stage, mitoses and the erythematous change described by Denton²³ as occurring in human pellagra were not observed. Congestion of the intestines is an observation that can be correlated with pellagra. Chromogenic urine and incontinence of urine, observed in some of our animals, are not prominent in human pellagra according to the experience of one of us (H. S. T.) with numerous pellagrins.

In our opinion, neither we nor other investigators preceding us have actually produced a disease in the rat comparable with human pellagra. All that can be said is that pellagra-like symptoms have been experimentally produced. If a true seasonal variation can be established, this might be of considerable importance. Jobling²⁴ emphasized the fact that sensitization to light may have an important place in the etiology of pellagra. It is possible that his work may have significance in relation to pellagrins suffering from vitamin G deficiency.

SUMMARY

Vitamin G deficiency was produced in albino rats on a variety of diets. The main symptoms observed were cessation of growth, loss of weight and dermatitis. Other accompanying symptoms noted in some animals were ophthalmia, chromogenic urine and incontinence of urine. No correlation was found between loss of body weight and the onset of skin lesions, and it is therefore concluded that the antidermatitic and growth-promoting syndromes are not identical. A seasonal variation was noted in the occurrence of the dermatitis.

Alopecia, ulceration of the skin, atrophy of the spleen and of the thymus, fatty changes of the liver and hemorrhages and congestion of the intestines were the main pathologic changes.

23 Denton. *Am J Trop Med* **5** 173, 1925.

24 Jobling and Arnold. *Etiology of Pellagra*, *J A M A* **80** 365, 1923.

General Review

BENZENE (BENZOL) POISONING

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This is an attempt to summarize what was published to December, 1930, regarding the action of coal tar benzene, C_6H_6 , on animals and on human beings. The effect of large doses resulting in acute poisoning can be considered fairly briefly, the more important action of small doses administered over long periods of time has been far more extensively studied, and here there are many records of experiments on animals and also of the experimental use of benzene in the treatment for leukemia. There are also a fair number of careful clinical histories of chronic benzene poisoning, always in industrial workers, and a small number of detailed reports of autopsies. In view of the importance and the unusually interesting character of chronic benzene poisoning there is a surprisingly small number of carefully studied clinical cases in the literature, and knowledge of the action of this poison must be gathered in large part from the experimental field.

Benzene, commercially known as benzol, is a colorless, limpid liquid, with a characteristic odor which is rather pleasant. It boils at $80.2^{\circ}C$, has a specific gravity of 0.899 at $0^{\circ}C$, is highly insoluble in water, is somewhat soluble in alcohol, and is an excellent solvent for rubber, gums, resins and fats of all kinds. The industrial uses are based on this solvent action. Pure benzene is not used in industry, the ordinary variety contains some toluene and xylene, perhaps olefins, paraffins, carbon disulphide, etc.¹

ACUTE BENZENE POISONING

Acute benzene poisoning has been the subject of study both experimental and clinical, but not nearly to the extent that has chronic poisoning, for the changes produced are not of so unusual a character. In acute poisoning benzene produces the condition characteristic of the action of an asphyxiating agent. It has a pronounced effect on the central nervous system, causing at first irritation, muscular twitchings, deepening of respirations, which are quickened at first and then slowed, quickening of the pulse rate, lowering of temperature and, in fatal cases,

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¹ See Final Report of the Committee of the National Safety Council, May, 1926

naïcosis, convulsions and death from paralysis of the respiratory center. The blood remains fluid for a long time after death (Lehmann, Heffter, Suiy-Bienz, Beinbauer). Lehmann's animals showed no characteristic changes at autopsy, no odor of benzene and no microscopic changes in the blood. If the lung cavity is opened promptly there may be an odor of benzene.

Kobert (p. 926) classed benzene under the heading, "Poisons Which Can Kill Without Causing Severe Anatomical Changes" and under the subhead "Poisons of the Central Nervous System." He quoted Simpson and Snow as having tested it "decades ago" as an anesthetic; they found that it could not be used for man because of muscular twitchings and other unpleasant symptoms.

Rambousek tested benzene on dogs and rabbits, finding the former more susceptible. No after-effects were noted in those that survived, nor was anything found after death in those dying of the effects, beyond a moderate hyperemia of the brain, lungs and mesenteric vessels.

Benech, in 1878, found that benzene produced glycosuria in guinea-pigs, but not in rabbits or in dogs (Kobert). Beinbauer called it a hemolytic poison, and so did Lewin in the 1897 edition of his "Toxicologie," but Kobert could not bring about the elimination of blood coloring matter in the urine by subcutaneous injection of benzene even in cats, although cats are unusually susceptible to hemolyzing agents.

Schmiedeberg, in 1881, studied the excretion of benzene, and found that when administered by mouth, it is excreted partly in the expired air without change and partly by the kidneys, not as phenol, but in the form of conjugated sulphuric or glycolonic acids. This conjugation of the oxidation products of benzene is a necessary condition for their appearance in the urine.

The earliest record of an autopsy in a case of acute benzene poisoning was published in 1888 by Suiy-Bienz. He found conspicuous bright red death spots, the blood was fluid and dark, there were large and small hemorrhages in the pleura and in the intestinal mucosa, general venous congestion, and a reddened lining of the air passages, which contained blood and mucus. The second autopsy did not come until eleven years later, when Beinbauer made one on a man dying of acute benzene poisoning and confirmed every detail of Suiy-Bienz's observations, but said in addition that the blood was lake-red, and that there was evidence of destruction of the red blood corpuscles. The body had a curious aromatic odor, but the tests for benzene were negative. The blood was weakly acid.

Even as late as 1907 deaths from acute benzene poisoning were rare enough to require Lewin to write a polemical article, defending his diagnosis of death from benzene vapors in a man who lived only ten minutes after he was rescued from a tank into which benzene was

dripping Buchmann, in 1911, reported an autopsy with typical results, i. e., wine-red spots on the skin, pronounced hyperemia of the internal organs and small hemorrhages in the pancreas. During the war Martland (1917) examined the bodies of two men who died from acute poisoning in the making of synthetic phenol. One showed cyanosis of the mucous membranes and finger-tips, cyanosis of the liver, spleen and kidneys, dilatation of the right side of the heart, which was filled with dark, fluid blood, pleural ecchymoses and small areas of acute interstitial emphysema in the lungs. The other one had, in addition, cyanosis of the brain, petechial hemorrhages in the pericardium and reddened and irritated bronchi. On section of the lungs a decided odor of benzene was given off. The urine contained an abnormal quantity of phenol, but no benzene.

The presence of phenol bodies in the urine was noted by Heffter and by Beisele and by Simonin, as well as by Martland. Beisele failed to find blood, albumin or hematoporphyrin. Simonin found urobilin, as well as diminished urea and diminished chlorides. In cases that are rapidly fatal, the search for phenol bodies fails, according to Heffter, for the change to conjugated acids is fairly slow.

Heffter, in 1915, reviewed twenty-one reports of cases of acute benzene poisoning from the German literature. The most characteristic change that is noted in animals is also found in man, i. e., dark red blood which remains fluid for a long time, but in which there is no evidence of hemolysis. Hemorrhages, usually punctate, are found in the lungs and pancreas, and in the gastric and intestinal mucous membranes. The abdominal organs show unusual congestion, and there is bloody mucus in the air passages. There are numerous bright red spots on the skin, there is no odor of benzene, and it cannot be detected chemically.²

Ziel told of three workmen who were overcome when the ventilation in a rubber sheeting factory was shut off, one of whom died. The body showed very bright red spots, and at autopsy a condition was found like that following suffocation, all the organs being overfull of blood. Ziel quoted Binder as having made similar observations in 1921: dark, fluid blood, edema of the lungs, congestion of all the organs, especially the abdominal ones, and many punctiform hemorrhages on the surface of the brain.

Floret (1926) found at autopsy numerous hemorrhages in the subcutaneous fat tissue, in serous membranes and in almost all the organs, some very large, some microscopic, the large occurring especially in

² See, however, Martland's case, page 7. Stuelp also found benzene in the brain after death from acute benzene poisoning (*Ztschr. f. Med. Beamte* **32**: 297, 1919).

the brain tissue and meninges. The blood was cherry red like that in carbon monoxide poisoning. This man lived fourteen days after an acute intoxication, long enough for severe anemia to develop, with fever, delirium accompanied by muscular twitchings, and cardiac weakness.

The records of a recent autopsy on a victim of acute benzene poisoning were sent to me by Martland. A chemist was found dead in a laboratory where benzene had leaked over the floor from an apparatus for the production of pyrimidin. A second man in the same room was still living when found and later recovered. The evidences of asphyxiation at autopsy were as follows: Cyanosis, fluid blood in the right side of the heart, with marked distention, and areas of acute interstitial emphysema in the lungs. All the other organs were normal. This autopsy was made while the body was still warm, before rigor mortis had come on. There was no distinctive odor in the lung cavity, nor in the brain. Parts of the brain, lung, kidney, liver, spleen and stomach were tested for benzene by A. E. Edel, toxicologist of Essex County, and benzene was found in the brain and lungs. The result of a test for methemoglobin in the blood was negative.

Although the usual outcome of acute benzene poisoning is either death within a short time or complete recovery, in a few instances there is evidence of lasting damage from the acute asphyxia. Genhard saw two cases of acute benzene poisoning in a chemical factory in Basel.

The first occurred in a chemist extracting pyrimidin with hot benzene. He had a slight attack of dizziness, which did not trouble him much until he went to bed. Then it became intense, with vomiting, recurring whenever he lay down. This lasted for over two days, so that the only bearable position for him was sitting up with the head bowed. He did not recover completely for twelve days, during which he suffered from uncertain gait and weakness of the legs. At the height of his attack there was cyanosis, his breath was aromatic and his pulse rapid and irregular, but there were no other symptoms.

The second case occurred in a weakly boy, aged 18, who after two days' work had severe dizziness, persistent cyanosis, marked weakness, headache, nausea, anxiety, dyspnea and sweating. Catarrh of the upper air passages developed, with slight fever, and eight days later an exanthem appeared over the back. At the end of twelve days he was still unable to walk.

At the same meeting at which Genhard's paper was read, Wyss reported a case of obstinate and intense dizziness following benzene poisoning: inability to stand, disturbed sleep with bad dreams and psychic depression.

Kobert told of a man who was painting the inside of a reservoir with bitumen and crude benzene. He became acutely intoxicated, as if from alcohol, and recovered, but later without any further exposure he developed pleurisy and catarrh of the lung and was never restored to complete health. One of Lewin's patients had an acute attack of

dizziness, a feeling as if he were drunk, pressure in the head, dyspnea, oppression of the heart and, when these symptoms passed over, a blowing heart murmur, yellow pallor and general nervous exhaustion

The histories of acute benzene poisoning in the literature reveal clearly the great variation in individual susceptibility to this poison, for it happens fairly often that the one who is exposed for the shorter period dies, while the one who is exposed longer and more intensely survives (Lewin)

CHRONIC BENZENE POISONING

Much more interesting than the acute form, resulting from a single severe exposure, is chronic benzene poisoning, which has been the subject of much more study both by means of experiments on animals and through clinical observations, supplemented in a minority of the cases by examination of the bodies of the fatally poisoned

EXPERIMENTAL POISONING IN ANIMALS

There is a fairly extensive literature on chronic benzene poisoning produced experimentally in animals. The first experiments of importance seem to be those of Santesson in 1897. Santesson had before him the task of determining the toxic substance in a solvent used by a group of women workers among whom were found nine with purpura hemorrhagica. The literature on coal tar benzene, which at that time and for years afterward was called either benzine or benzol, but practically never benzene, made little, if any, distinction between the coal tar distillate and petroleum benzine. Thus Santesson quoted Korschenewski as saying that both petroleum and coal tar "benzine" were capable of causing hemorrhage, as shown by purpura and hemorrhage in men working in the petroleum fields of Baku, notably in one who died with purpuric spots, bloody expectoration and bloody vomit. At that time it was not known that the oil of Baku is rich in coal tar benzene.

Santesson used rabbits and administered the benzene (1) through the skin by poultice, (2) through the inhalation of vapors and (3) by subcutaneous injection. The method of inhalation was unsuccessful, but the other two methods resulted in death, the third the more quickly. Santesson assumed that the vapors did not count in the death of the poulticed animals because of the failure of those experiments in which vapors only were administered. He obtained the same effects from crude benzene as from pure, but the crude was the more toxic. He called the crude liquid benzine and the pure, distilling at from 80 to 85 C, benzol. Chronic poisoning was characterized by hemorrhages in the pleura, the lungs and the mucous membrane of the stomach and intestines. In animals poisoned through the skin, hyperemia and edema of the subcutaneous tissues showed the passage of benzene through the

skin The cause of the hemorrhage in organs and mucous membranes he believed, was not a fatty degeneration of the vascular epithelium, because this was absent in rabbits He thought that embolism might be the underlying cause There is no record of any blood counts having been made in these experiments

Between the epoch-making paper of Santesson and the next mile-post, Selling's publications, little experimental work was done, and the most noteworthy contribution adds hardly anything to the picture This was the work of Langlois and Desbouis, who, in 1907, treated rabbits, guinea-pigs and pigeons with prolonged inhalations of volatile hydrocarbons, the exact nature of which it is impossible to make out with certainty They spoke of benzol and of moto-naphtha, which apparently had the same effect Benzol they defined as a mixture of benzine and toluene The vapors were administered in two concentrations, namely, 16 cc and 24 cc per cubic meter of air The most conspicuous effect was true polycythemia, marked and constant, in guinea-pigs, pigeons and rabbits—most marked in the first—failing to appear in dogs and cats This increase in red blood cells consisted in a progressive rise from 5,250,000 to 8,000,000 in forty-five days, if the dose was moderate, and in five days with a heavy dose Even a single administration of 24 cc per cubic meter of air for five hours was followed by a rise of 1,000,000 red cells A fall in the temperature of the body was also noted The descent of the red cell count described a regular curve, which reached the normal in guinea-pigs in fifteen days This could not be attributed to concentration of the blood, for the white count was little altered, slightly decreased, if anything, and there was no increased density of the serum, nor was it due to a massing of red blood cells in the peripheral blood, for the heart blood showed the same picture The increase in hemoglobin was not proportional to the increase in the number of red cells, and no nucleated red cells were found

The observations of Langlois and Desbouis, especially with regard to polycythemia, were never confirmed As to their failure to produce leukopenia of any notable degree, it must be said that Selling had the same experience when benzene was administered by inhalation

Selling's work in the years from 1910 to 1911 established certain facts with regard to the toxicology of benzene which were confirmed by many experimenters following him His work stands out above that of any other, not only in the clinical, but in the experimental, field Practically all subsequent students have used his technic and, as a preliminary to the pursuit of their own particular problems, have repeated his experiments and confirmed his results as to the essential features The most important effect of benzene when given subcutaneously to animals (equal parts of benzene and olive oil were used by Selling) is leukopenia, the

fall in the count of red cells being far less striking. The most important change found postmortem is aplasia of the bone marrow. Selling showed that by means of injections of benzene with olive oil the leukocytes can be diminished in number to the point of almost complete disappearance from the peripheral circulation and that they may afterward rise to the normal level with recovery. Thus leukopenia reaches an average of 50 per cent at the end of three days and of 75 per cent at the end of four days, with total disappearance some hours before death. Occasionally there is a slight increase in the white count at the outset (Selling reported this in three animals). In the early stage there is an outpouring of large numbers of normal and abnormal leukocytes, of either the large lymphocyte type with large, deeply staining nucleus and narrow basophil protoplasm, or the same cell with an irregular nucleus and varying degrees of basophilia. Myelocytes were seen by Selling in one case only. The white cells fall on an average 2,200 within twenty-four hours after the first injection and 50 per cent after the second. If the experiment is stopped when the white count has reached 40 to 720, the animal dies, sometimes with the same count, sometimes with a lower. Usually after injections of benzene are stopped, there is a preliminary rise of the white count, then a fall, then a slow rise to normal.

The fall in the red cell count is much less striking, unless benzene is administered over a far longer period. In a small percentage the red count shows a rise following the first injection, perhaps still greater after the second, but always after the third it goes back to the original level or falls below. Sometimes the fall comes after the fourth or the fifth, but in other cases the red count remains constant. The average loss at the end of eight days is only 16 per cent, while the loss of white cells averages 92 per cent. But in recovery, while the white cells are returning to normal, the red cells show no similar tendency.

The disappearance of the white cells, according to Selling, is not due to accumulation in other parts of the circulation, because they are absent from the vessels throughout the body.³ Therefore, they must have been destroyed by the poison or have undergone natural death with no regeneration. But 75 per cent of the white cells would not die naturally in three days, and the degenerated forms of leukocytes, both mononuclear and polymorphonuclear found in the circulating blood argue for poison. The polymorphonuclears suffer most, in correspondence with the severe injury in the marrow as compared with that in the lymphadenoid tissues, just the reverse of what occurs in exposure to roentgen rays. The red blood cells are less affected, no more than can be accounted for by natural death of cells. The increase of the

3 See, however, Pappenheim and also LeNoir and Claude, p. 19

pigment content of the spleen is not great and may be accounted for, in part at least, by the destruction of nucleated red blood cells in the marrow. Selling quoted Heinecke as observing the same thing, in experiments with 100 mg. benzene. In both his and Heinecke's experiments there were only slight changes in the red blood cells, in spite of the advanced degree of aplasia of the marrow. The red blood cells return to normal more slowly, yet in the early stages of the regeneration of the marrow the erythroblasts are often very much more abundant than the granulocytes.

Selling emphasized the stimulating effect of benzene on the marrow cells. Stimulation and destruction are constantly associated, the former prevailing at first, the parenchymal cells increasing rapidly, especially the more highly differentiated cell types. But this hyperplastic marrow begins to show well marked destruction of cells by the end of the second day, and the destruction increases, leaving empty spaces with edematous reticulum and wide capillaries, till only isolated cells are left, and after about the ninth injection the marrow is almost wholly aplastic. Erythroblasts, granulocytes and megakaryocytes are all affected, but in the polymorphonuclear amphophils the proportion of degenerated cells is always least. They disappear rapidly, however—probably being swept into the circulation. Small lymphocytes and polyblasts are found in considerable numbers and have the greatest resistance, persisting and apparently increasing after all others have been destroyed.

Selling's "ascending" series comprised those animals in which regeneration took place after aplasia of the marrow. In the early stages of regeneration, islands of cells appear in the reticulum, erythroblasts chiefly or granulocytes or large lymphocytes, which are abundant, and between these islands lie small lymphocytes and polyblasts. Other collections of cells form cords in radiating bands. Megakaryocytes are present, scattered or in bands. As regeneration progresses, the younger cells—the large lymphocytes, myeloblasts and megaloblasts—form an ever diminishing proportion. Regeneration can occur after an advanced degree of aplasia. Selling believed that the small lymphocytes and polyblasts play the chief rôle in the regenerative process, the steps being from small lymphocyte to large lymphocyte and then to megakaryocyte.

The lymphocytes in the follicles and medullary cords of the lymph glands show degenerative changes, following injections of benzene, within twenty-four hours, increasing as the experiment goes on. Large phagocytic cells pick up part of the debris of these cells. The follicles are progressively emptied, and the sinuses dilate, but aplasia is never complete. The changes are less marked than in the marrow. Regeneration is complete in from ten to fifteen days, but there may be some

fibrosis resulting from the irritating action of benzene. The changes in the spleen are similar to those in the lymph glands, but during regeneration, especially during the later stages, myeloid metaplasia occurs, with myeloid cells of all types. These are, however, relatively few in number, and at this stage the marrow is hyperplastic. Therefore, the myeloid metaplasia of the spleen can have little significance as a compensatory phenomenon.

Selling stated positively that benzol is a leukotoxic poison, destroying not only the tissues that produce leukocytes, but also the leukocytes in the circulating blood since their decrease comes on too rapidly to be accounted for by natural death or by the injury done to the tissues.⁴

A well known byproduct of the publication of Selling's studies was the deliberate utilization of the leukotoxic action of benzene to reduce the white cell count in leukemic patients. The results obtained in these experiments on human beings are discussed in another section, but a secondary effect was the stimulation of interest in the physiologic action of benzene and a sudden outburst of articles on benzene poisoning in animals. Many of these were confirmatory of Selling's work, but some new details were added. Thus Secchi administered benzene by inhalation, injection and ingestion, and produced not only an enormous diminution of leukocytes, but a fall of hemoglobin to 50 per cent or less, a loss of red cells, a fall in specific gravity, a low color index, and poikilocytosis and stippling. The viscosity of the blood was increased when the benzene was administered in vapor form. At autopsy Secchi found that acute poisoning caused intense congestion of all the organs, and that chronic poisoning caused fatty degeneration and numerous hemorrhages, subpleural and into the mucosa of the intestinal tract and the genital tract.

Brandino's experiments are interesting, and since they are not available to most English-speaking students, I will venture to give them in detail.

He studied the lymph glands, marrows and spleens of dogs and rabbits to which benzene had been administered by inhalation, by ingestion and subcutaneously. In the lymph glands there is a notable destruction of the lymphocytes, which show karyolysis and karyorrhexis and fragmentation of chromatin. The debris is taken up at first by phagocytes, then these cells disappear, there is retraction of the reticulum and flattening of the follicular region, while the peripheral and medullary canals dilate. The medullary tracts are much less affected than the

⁴ Ronchetti also said that leukopenia comes on quickly, before the leukopoietic organs could have undergone marked involution. Therefore, one must add to atrophy of these organs intensification of the destructive processes in the circulating blood.

follicles, which are finally reduced practically to the reticulum. If the benzene is stopped, however, there is complete regeneration. Similar changes take place in the spleen, but here also there may be complete regeneration, during which myeloid metaplasia occurs. At the same stages there is less degeneration of cells in the spleen than in the lymph glands, and it is not so marked in the malpighian corpuscles as in the stroma. In the former the cells disappear first at the periphery, leaving a compact mass of cells at the center which, with the progress of poisoning, diminishes gradually till all the lymphocytes are gone and the malpighian body is recognized only by the disposition of the reticulum and the central vessel.

Brandino also found that benzene acts as a stimulus to the marrow, as well as a destroyer. At first the former action predominates, causing a rapid and notable increase especially of the most highly differentiated blood cells, while the myelocytes and megaloblasts are less affected. After the third or fourth injection hyperplasia begins to yield to destruction, till only narrow cords of cells are left, with edematous reticulum and dilated capillaries between. Then regeneration begins, which progresses rapidly and goes on to hyperplasia. The most resistant elements are the small lymphocytes and the polyblasts, which are found in the marrow after all others are gone. The spleen in advanced stages shows myeloid cells of all types.

Orzechowski (1929) noted that all experimenters had agreed that the red blood cells are not affected in chronic benzene poisoning, which is hard to understand, since more recent work was shown that the red corpuscles and the leukocytes have a common mesenchymal origin⁵. He employed Selling's technic, using rabbits, and in sixteen experiments found no change in the red cell count or in the character of the cells. Stippling was seen in one animal only, the loss of hemoglobin (Sahli) was slight, staining was normal. Therefore he held it to be evident that benzene does not attack the tissue which forms red blood cells. The histiogenic leukocytes (monocytes) were injured, but nothing like so much as the granular polymorphonuclears. The platelets were normal, and the clotting time in the warm chamber was normal in most cases. The leukocytes fell from 13,900 on the first day to 1,300 on the seventh and to 400 on the eighth day, following the last dose.

5 It is not, however, strictly true that all students of experimental benzene poisoning found an absence of attack on the red blood cells. Not only Secchi (see a foregoing paragraph), but Fontana, found a lowered red cell count and a loss of hemoglobin in animals, although this was not so striking as the loss of white cells. Mauro found anemia with poikilocytosis and anisocytosis in the late stages, and Duke, in seeking to produce a loss of platelets, produced also severe anemia, with benzene. In Weiskotten's experiments with inhalation of benzene, loss of red cells was observed (see page 31).

Oizechowski concluded that the severity of the attack of benzene is on the granulocytes, and he pointed out that this corresponds with what occurs in the central nervous system, where it is a rule that the latest cells in phylogenic and ontogenic development are the most vulnerable to all injuries

Wallbach endeavored to distinguish the action of benzene in producing leukopenia from that of thorium X and that of x-rays, soft and hard. Benzene has a destructive action on the spleen and lymph nodes and also inhibits the formation of new cells by the bone marrow and the further differentiation of immature cells, so that there is a delivery to the circulating blood of granulocytes, polymorphonuclear with a swing to the left (Arneth). Thorium X causes a release of leukocytes into the blood stream and an inhibition of the formation of new cells but not of differentiation of immature cells, therefore the leukocytosis in this case is of mature cells. Soft x-rays do not diminish the white cell count, but there is a conspicuous increase of eosinophils and of mast cells, while hard rays injure the lymphatic tissue, although a marked leukopenia is never produced. The increase of eosinophils and of basophils is not as great with hard rays as with soft

Pappenheim and Neumann both challenged some of the observations of Selling. Thus Pappenheim believed that the decrease of leukocytes is not so great as examination of the peripheral blood suggests, for he found in rabbits that at a stage when the white cells had almost disappeared from the circulating blood they were found in some cases still very abundant in dilated capillaries of the liver, lungs, spleen and kidneys⁶

Neumann was unable to find fatty degeneration, as Selling found, but always found a striking hyperemia of the spleen, not mentioned by Selling. The spleen showed aplasia, but also pigmentation. The bone marrow was hypoplastic, as described by Selling, but Neumann never found the numerous small lymphocytes and polyblasts described by Selling, and found much more pigment. Some animals had pigment in the spleen, others in the liver and marrow, and the quantity was enormous in comparison with the controls. This could not be the result of chance, but hardly the result of blood destruction either, because of the slight loss of red blood cells, especially in that animal which had the largest amount of pigment.

Neumann emphasized the great variations in individual animals in their reaction to benzene, which explains the varying results in patients treated with benzene. For example, two rabbits were given the same

⁶ The only other observers to note an accumulation of leukocytes in the internal (intestinal) capillaries were LeNoir and Claude in a man dying of chronic benzene poisoning.

dose, the second lived seven days longer than the first. A third animal had a larger dose, but lived longer than the first. A fourth had the smallest dose and died the most promptly.

The organic lesions noted in animals are, on the whole, more marked and extensive than those found in most of the autopsies on human beings (see page 64). Chassevent and Gairner found in guinea-pigs congestion of the peritoneum and of the abdominal organs and not only ecchymoses, but ulcerations, in the gastric mucosa at the niveau along the artery. Klemperer and Hirschfeld found more or less severe destruction of marrow and extensive necrosis of liver and kidneys. Pappenheim also noted necrosis of the liver in rabbits and severe injury to the parenchyma of the kidneys.

Mention must be made also of some observations with regard to the action of benzene made by certain investigators in the course of their work on general problems. Underhill and Harris, working on creatine metabolism, tested the effect of injections of benzene with oil in rabbits and found that benzene not only acts on the blood elements, but that it exerts a catabolic influence on the body tissues as a whole, as manifested by a sharp rise in the excretion of creatine and total nitrogen within a very short period after subcutaneous injection, far in excess of that found in rabbits under ordinary starvation.

Jaffé examined the excretion of benzene in rabbits and dogs, giving them a daily dose of from 2 to 3 Gm. by mouth. He found that it was excreted in the urine partly as muconic acid by oxidation of the ring, C_6H_6 plus O_2 . Following him Fuchs and Soos isolated muconic acid from the urine of a leukemic patient who under Koranyi's treatment was being given benzene. He excreted from 3 to 5 Gm. of muconic acid in twenty-four hours. These authors believed that the production of muconic acid as an intermediate stage may be assumed to take place, but its detection is prevented because of the ease with which it forms combinations and changes to other bodies, such as acetone.

The prolonged bleeding time and clotting time in human benzene poisoning and the failure of the clot to contract led students of the physiology of the blood to study this feature of its toxicology. Duke found in rabbits a rapid rise in the platelet count, followed by a rapid fall. Severe anemia went with this, and at autopsy the marrow was found to be almost completely aplastic, megakaryocytes were hardly to be found. In large doses, 5 cc., benzene acted first as a stimulant, then as a poison to the platelet-forming organs, causing first a rise, then a fall in the count. In small doses, 2 cc., it acted only as a stimulant causing a gradual rise in platelet count, which later fell but not below the normal. In every instance, human and experimental, in which the platelet count fell to a low level (61 000 was the lowest) purpura

hemorrhagica was observed. The reason for the rapidity of the rise and fall in the number of platelets is to be found in the short life of the platelet.

Hurwitz and Drinker studied "the factors of coagulation in the experimental aplastic anemia of benzene poisoning." In addition to their observations with regard to the clot-forming substances in the blood, their work brings out clearly the contrast between clinical and experimental benzene poisoning already pointed out by Selling and others. Benzene has an important influence in reducing the circulating prothrombin, but antithrombin and fibrinogen fluctuate little from the normal, results which are in harmony with proofs recently discovered that blood platelets contain prothrombin. The latter originates from the megakaryocytes of the marrow, but other tissues also play a part in its formation. Any toxin which diminishes the number of platelets diminishes the available prothrombin in the circulating blood. In most instances in which the circulating prothrombin is diminished, aplasia of the bone marrow occurs. The appearance of an extreme aplasia without fatal diminution of prothrombin suggests (1) that other tissues or organs are concerned in its formation, or (2) that a minimum amount of myeloid tissue is sufficient to maintain the quantity of prothrombin above a dangerously low level.

These writers used rabbits and followed Selling's technic. Benzene was shown to be a myeloid tissue poison. Their experimental animals did not show marked hemorrhagic features and did not as a rule show prolonged bleeding time or bleeding from the gums and mucous membranes, etc. In a few instances at autopsy the blood remained fluid a long time. In spite of the absence of hemorrhage, striking changes were found in the blood, in the formed elements and in the prothrombin, though not sufficient to cause a clinical picture of hemorrhagic disease. They confirmed the observations of Selling and of Duke, viz. a rapid disappearance of the white cells from the peripheral circulation, sometimes after an initial rise, red blood cells much less affected, sometimes not at all, in most cases reduced by 50 per cent, platelets showing the same general reduction, but to a less extent, remaining at a high level after the white cells have almost disappeared from the circulation. In only one animal were the platelets low enough to produce symptoms of a hemorrhagic disease.

Selling thought that the polymorphonuclear amphophils in the marrow are more resistant than the large lymphocytes, myelocytes, erythroblasts and giant cells. Hurwitz and Drinker suggested that either the megakaryocytes of the marrow regenerate very rapidly or they are more resistant to the action of benzene than are the forerunners of the polymorphonuclear leukocytes and erythrocytes.

The effect of benzene on the formation of antigen was tested in 1914 by Rusk in California and by Schiff working in Heffter's laboratory in Berlin. Rusk injected 1 cc of benzene per kilogram of body weight into rabbits either before or at the time of the injection of antigen and found a decided reduction in the formation of lysin for sheep's corpuscles and of precipitin. Schiff gave guinea-pigs intraperitoneal injections of 0.01 cc of benzene before an injection of antigen and found that there followed only slight leukocytosis and increased sensitivity to a second dose of antigen, while if he gave 0.03 cc, leukopenia developed, and sensitivity was diminished.

Simonds and Jones studied the curve of the production of antibodies in animals exposed to the x-rays, which exert a destructive effect, especially on the lymphadenoid tissue, and in animals treated with benzene, which exerts its chief effect on the bone marrow. For antigen they used washed dog's corpuscles and killed typhoid bacilli, and studied the degree of hemolysis and of agglutination. There was a high death rate in the animals treated with benzene, for they succumbed readily to spontaneous infections, and when the white cell count fell to 1,000 or less, they died even without evidence of infection. Benzene was given in doses of 1 cc per kilogram of body weight in 2 cc of olive oil, subcutaneously.

They found that while the most pronounced destructive effect of benzene is on the polymorphonuclear leukocytes, the lymphocytes are also affected. The power to produce hemolysins for dog's blood is much reduced by benzene, as is also the production of agglutinins and opsonins, in that order. They reasoned that the part of the blood-making system which has to do with the production of erythrocytes may be a factor of some importance in the formation of hemolysins, for the curve of the latter was similar in two rabbits with leukopenia and in the one with leukocytosis, but in all three animals the erythrocytogenic power was affected—as shown by the absence of nucleated red cells and stippled cells. The agglutinating power of the blood for killed typhoid bacilli was only from one half to one tenth of the normal, and the loss was greater in the animals treated by injection of benzene than in those exposed to the x-rays and was not in proportion to the leukocyte count. Opsonins were diminished by benzene but not so much so as agglutinins.

The fact that benzene had shown a selective action on tissues and cells that are concerned in the defense of the body against infection led Hektoen to test its action on the production of antibodies and on the activity of leukocytes. He used benzene and olive oil in equal parts for hypodermic injection into rabbits which had had, or were to receive, 30 cc of sheep's blood in the peritoneal cavity. A quantitative determination was then made of the newly formed lysin and precipitin. Hektoen confirmed the results of Selling and others as to leukopenia,

especially of the granular leukocytes, preceded sometimes by a leukocytosis of moderate degree after the first injection. There was also in a number of animals a second increase in the leukocyte count, followed by a secondary fall before a return to the normal figure (see Weiskotten). The death rate was high in animals with profound leukopenia, and the marrow was found to be poor in cells. The loss of red cells was not great.

The production of specific precipitin and lysin was greatly reduced, but the course of antigen in the blood appeared the same in benzenized animals as in controls. At the height of the production of antibodies the injection of benzene appeared to have but little effect on the leukocytes of the blood and on its antibody content. That benzene acts on the elements that elaborate antibodies and that leukocyctogenic centers are concerned in this elaboration was indicated not only by the reduction of antibodies and of leukocytes in the rabbits, but also by resistance to this effect when the production of antibodies was at or near its height, and by the leukocytosis and increased formation of lysin in dogs under the influence of small doses. Just how benzene interferes with the elaboration of antibodies whether by direct injury to the cells or possibly by modification of enzyme action, is still a question. The action of benzene does not show that certain specific elements are concerned in the elaboration of antibodies because its action is too general, affecting, it is true, the granular leukocyctogenic centers most, but the lymphocytes and the erythroblasts, as well. Hektoen concluded that benzene may lower the anti-infection powers of the body in at least three ways: by reduction of antibodies; by reduction of the number of leukocytes; and by reduction of the phagocytic action of the leukocytes.

These conclusions were confirmed by experiments on the course of infection in benzenized animals. Thus Winternitz and Hirschfelder, while working on pneumonia, tested the effect of injections of benzene on the resistance of animals to pneumococci. They first reduced the white blood cells by means of benzene and then produced pneumonia by intratracheal inoculation with cultures of virulent pneumococci, and they found a marked reduction of resistance to the infection. The average duration of life after inoculation of the control animals was sixty-one hours, while in the animals treated by injection of benzene it was only twenty hours. The leukocytes were reduced in six rabbits to from 280 to 880. There was no difference in the gross appearance of the lungs in the two groups, but microscopic examination of the pneumonic exudate showed, in the benzenized rabbits, only occasionally a polymorphonuclear leukocyte or undifferentiated mononuclear cell, although the exudate contained the usual number of red blood cells and fibrin.

White and Gammon, inoculating rabbits with tubercle bacilli and administering benzene by inhalation, found that the latter lowered the resistance of these animals as compared with controls, but were unable to find the explanation of this result

Camp and Baumgartner studied the effect of benzene on the course of inflammatory processes produced by chemical irritants, by heat and by the injection of unsterilized foreign bodies. They used Selling's method, injecting 2 cc per kilogram daily till the leukocyte count fell below 1,000, then smaller doses. If they gave smaller doses from the first, there was a marked loss of weight, but without pronounced leukopenia. The best results were obtained by two or three doses of 2 cc, then from two to five doses of 3 cc till leukopenia appeared, then doses just large enough to keep the white count low. Inflammation was produced by (1) cotton oil rubbed into a deep scratch on the ear, (2) intramuscular injection of an aqueous solution of carmine and (3) immersion of the ear for three minutes in water at 55 C. Non-benzenized animals were, of course, used as controls.

They did not find the initial rise in the white cell count described by Selling, but if one dose of the series was omitted, a rise would occur. Cotton oil normally causes a marked inflammatory reaction in from twenty-four to forty-eight hours, edema, and dense infiltration of the tissues with polymorphonuclear leukocytes. In the animals treated with benzene no gross changes were found, except in one, in which there was pronounced edema. In this same animal microscopic examination of the area showed a few lymphocytes, in the others, no leukocytes were to be seen. Masses of bacteria were found, evidently multiplying rapidly in the tissues and meeting little or no resistance. The most essential histologic difference between the benzenized animals and the controls was the absence of leukocytes in the inflamed areas.

Heat of 55 C caused in the control animals rapid swelling and congestion of the ear, under the microscope edema, congestion and a considerable number of leukocytes were seen, but the latter were much less numerous than in the first series. In the leukopenic animals there were immediate swelling and congestion, but no collection of leukocytes. In the series treated by injection of carmine, microscopic examination of the controls showed that the particles of carmine soon became surrounded with polymorphonuclear leukocytes, which ingested the particles, and that then by the end of the second day a proliferation of connective tissue began. In the leukopenic animals, only two had any leukocytes around the masses of carmine and one of them had a terminal rise in the white cell count to 3,800, the other to 1,000. There was no proliferation of connective tissue in any. The carmine was not sterilized, none of the controls showed any bacteria in the tissues, while almost

every one of the leukopenic animals showed masses of bacteria in the collections of carmine and in the surrounding tissues

These experiments showed that in almost every instance there is no leukocytic exudate in rabbits which have a severe leukopenia, and that there is an absence of antibacterial bodies "which may not be due entirely to the destruction of the leukocytes, since benzene probably has a generally cytotoxic, as well as a leukotoxic, action" Benzene was given to one of the rabbits with severe leukopenia which had developed a large abscess in the neck It died when the white cell count fell to 600, but there was no effect on the abscess and benzene did not destroy the leukocytes in the abscess Congestion of the blood vessels and edema occurred independently of the leukocytes When the leukocytes were below 1,000, croton oil and heat produced no leukocytic exudate in the tissues of the ears, and carmine none in the muscles

Weiskotten and his colleagues published, between 1915 and 1923, a series of studies covering many aspects of benzene poisoning, their special interest being in the therapeutic use of benzene as a leukotoxic agent In the first article (1915) they told of testing the compensatory function of the spleen in regenerating erythrocytes and leukocytes by giving benzene to normal and to splenectomized rabbits They found in both the usual rapid decrease in leukocytes, with a primary rise in the count, followed by a secondary fall and a secondary rise to a permanent level The polymorphonuclear leukocytes were chiefly affected With the primary fall went a moderate, but definite, fall in erythrocytes, but after this the erythrocyte curve appeared to progress independently of the leukocytes, and in most animals was unchanged during the second fall in the leukocyte count There was no essential difference in the blood curves of animals the spleens of which had been removed and of those with spleens intact, showing that in rabbits the spleen has no essential function in the destruction of leukocytes and erythrocytes, nor in their subsequent regeneration The myeloid metaplasia of Selling is of no great importance as a compensatory phenomenon

The second article (1916) deals in detail with the "diphasic" leukopenia "In all cases where animals survived the primary fall in the leukocyte curve there followed a primary rise which in all instances reached a normal level, and in many the original level (This is the 'protophase') This primary rise was in each instance, independently of any further injection, followed by a secondary fall and then a rise to a normal level In the secondary fall ('deuterophase') the leukocytic curve in almost all instances reached a level nearly as low as that reached in the primary fall, and in some instances even lower" "The deuterophase of the diphasic leukopenia was not accompanied by any

changes in temperature curve except in one animal which had very low counts at the primary and secondary falls, in which the temperature rose at the climax of both falls "

The mortality was practically as great during the second fall as during the first. In all animals surviving the second fall the leukocyte curve returned to the normal level and there was no further fall. Between the first injection and the onset of the deuterophase there was a period of from eight to eighteen days corresponding closely to the period required for sensitization after the injection of an antigen and suggesting that the deuterophase might be the result of an antigen-antibody reaction, but no changes in the temperature occurred and there was no difference between the protophase and the deuterophase.

The third article, by Brewer and Weiskotten (1916), treats of the urine in benzenized animals. During the first twenty-four hours after the first injection the total of the phenols of the urine increases and still more after the second injection. This increase persists forty-eight hours after the last injection, then there is an abrupt return to normal.

In Weiskotten's fourth article (1917-1918) spontaneous infection occurring in benzenized animals was studied with special reference to its effect on the diphasic leukopenia. In four rabbits the leukopenia did not appear, and it was found that during the daily subcutaneous injections, acute infection had developed, and in two of these animals it seemed that it might even have been present before the experiment and to have been "lighted up" after the injections began. In none of these did diphasic leukopenia occur, and in only one, aplasia of the marrow. The percentage of polymorphonuclears in these animals, instead of falling, rose in all to from 83 to 97 per cent before death. In three animals there was also leukocytosis.

The fifth article (1919) describes the diphasic leukopenia as being accompanied by a relative increase in polymorphonuclear amphophils. The small mononuclear cells are absolutely decreased at the climax of the first phase to a greater extent than are the polymorphonuclear amphophils. At the end of the second phase the total leukocyte curve reaches a level somewhat lower than that existing before the injections began, and this is due to the failure of the mononuclears to rise to as high a level as before injection. This is the only observation of its kind in the literature.⁷

Weiskotten's experiments to this point were made with injections of benzene. Experiments with inhalation (1920) were then made on

⁷ The reverse was found by practically all experimenters, with the exception of Fontana, who stated that although the lymphocytes survive longest in most cases, those that develop very rapidly may not show this inversion of the leukocytic formula.

11 rabbits, which died on various days from the first to the sixty-ninth. One of them lived till the fifth day after the experiment had ceased, another, till the sixteenth. The results were somewhat different from those obtained in the earlier series. The fall in the white cell count was as sharp, but never went as low as 1,000, even if the experiment continued 53 days. Attempts to bring about a more marked leukopenia by higher concentration of benzene were fatal to the animals. After the experiment ceased, the low count persisted for from 12 to 36 days, then gradually, in from 36 to 51 days, rose to a permanent level, which was considerably lower than that existing before the experiment began, and which was maintained as long as the counts were made, in no instance returning to the normal level even after from 368 to 458 days. The average count for three animals was 11,302 before and 6,166 after the experiment. There was no deutero-phase, as after injections. The red cells fell to a low level in from 6 to 16 days, and stayed there as long as the experiment continued, but with no tendency to fall lower, and after the experiment ceased they rose to the former level in from 15 to 24 days. The average fall was from 6,126,000 to 4,947,000.

In his last article, published in 1923, Weiskotten stated that the diphasic leukopenia is a direct result of the necrosis of bone marrow produced by benzene, and that the final return of the leukocytes to a normal level is due to active regeneration of the leukoblastic elements of the marrow. The erythroblastic elements of the marrow also undergo necrosis and regeneration, but the circulating red corpuscles are apparently little affected, and their curve shows slight changes, if any, following injections of benzene. There is a temporary increase of thrombocytes in the circulating blood at the beginning of the experiment, and as the resulting necrosis of the bone marrow gradually progresses, there is a progressive decrease in thrombocytes which lasts during the entire period of necrosis. Active regeneration of the bone marrow is accompanied by a marked increase in the number of thrombocytes, which passes the normal limit and then falls to normal, thus furnishing additional evidence of the formation of thrombocytes in the bone marrow. The histologic examination of the marrow of animals dying or killed at times coincident with the beginning of thrombocytosis shows large numbers of megakaryocytes in the regenerating marrow.

EXPERIMENTAL POISONING IN MAN

The action of benzene has been studied by a number of observers in connection with its therapeutic use in the treatment for various forms of leukemia. Its use was first advocated by Koranyi in 1912, and he gave it greater publicity at the International Congress of Medicine in

London in 1913, when he reported on the results in eighty cases, not all of which were his own. He noted that high doses may destroy the red blood cells, whereas the proper dose stimulates their production up to a count of 6,000,000. An overdose or too prolonged treatment may cause hemorrhages in the skin and mucous membranes, anemia of a high grade, fever and almost complete disappearance of leukocytes, i. e., a typical picture of aplastic anemia or thrombopenic purpura, which is always fatal. Another danger is the continuance of the effect of benzene after the dose is stopped.

Billings, in 1913, reported favorably on this form of treatment in five cases, but also warned against possible bad results. He found that there was a tendency first to a rise in the leukocyte count, followed in from ten to fourteen days by a rapid fall and by a diminution in the size of the spleen and liver, more rapid than with treatment by the x-rays alone. Usually at this stage there was also an increase in the red cell count and in the hemoglobin, but the effect was not so marked as on the leukocytes. The effect was more rapid in lymphoid, than in myelogenous leukemia, with a rapid fall in the white blood cells, which were seen in blood smears to undergo early and marked degeneration. Spiegler, in 1914, administered benzene for three weeks to a woman with myeloid leukemia, with decided success. She went home and without authorization kept on with the benzene for five weeks more (the quantity is not given). She returned to the hospital very anemic, with a count of 2,600,000 red cells, the white cells, which at the outset had numbered 150,000, were now only 1,400, almost all of them lymphocytes, none myelocytes. This change came without any diminution in the size of the spleen. Three months later she had bleeding from the gums and suffusion of blood under the skin. The cell count was about the same, but the blood did not clot. At one count the leukocytes numbered only 400. The axillary temperature was from 37 to 39 C (98.6 to 102.2 F). Toward the end, ulcers appeared on the epiglottis, and ten days before death the first hemorrhage occurred. The granular leukocytes practically disappeared. This change could not be spontaneous, for myeloid leukemia never changes to leukopenia. It must have been the result of the action of benzene, which injures myeloid, far more than lymphadenoid, tissue. Spiegler quoted Klein on a case, also of myeloid leukemia, in which the leukocytes sank from 988,000 to 1,720 under benzene therapy.

Other cases described in the literature are those of Schmidt, Kilyfi and Neumann. The last named described the case of a man who, after improving under the treatment with benzene, with diminution of the leukemic tumors and a fall in the white count from 56,000 to 5,300, suddenly grew worse, fever, hemorrhage and leukopenia developed,

followed by death. The marrow was aplastic just like that in the experimental benzene poisoning of Selling.

Ronchetti and Stein found in leukemic patients treated with benzene a disappearance of the nucleated red blood cells from the circulating blood, even when there was no intolerance of the cure. Ronchetti said that Fontana found that basophil red cells disappeared. The fall in the white cells in benzene therapy affects first the immature forms, and its action is quicker and intenser in leukemic persons with many immature white cells than in nonleukemic persons, as shown in the experiment of Vaquez and Jacoul, who tested it in a normal man and in a patient with myeloid leukemia. In the former the white cells fell from 7,800 to 3,000, in the latter, from 800,000 to 16,000. Ronchetti himself administered benzene to a woman with Hodgkin's disease, who recovered when all else had failed. In three weeks the white cells had fallen from 8,906 to 260. The patient had chills and fever, nosebleed and disappearance of platelets, but this was followed by a rise of the white cell count to 5,312, a reappearance of platelets and recovery from the benzene poisoning. According to Ronchetti, this shows the action of benzene to be toxic to the circulating leukocytes and platelets rather than causing atrophy of organs, or the recovery would not have been possible.

(To be Continued)

Notes and News

Popular Science Monthly Award for Achievement in Science—The first annual award of \$10,000 "for the current achievement in science of the greatest benefit to the public" has been divided between George H. Whipple, professor of pathology in the University of Rochester, and George R. Minot, professor of medicine in the Harvard Medical School, in recognition of work on the influence of the liver on blood regeneration and of the application of liver extracts to the treatment of pernicious anemia.

University News, Promotions, Registrations and Appointments, etc—Hugh E. Burke has been appointed director of the research laboratory at the New York State Tuberculosis Sanatorium, Ray Brook, succeeding David T. Smith who resigned to become associate professor of medicine at Duke University.

Charles Krummurede, assistant director of the research laboratory of the Health Department of New York City and professor of hygiene and bacteriology in New York University, has died at the age of 51 years.

The William Wood Gerhard Gold Medal of the Philadelphia Pathological Society was presented on Jan. 8, 1931, to Simon Flexner, director of the Rockefeller Institute for Medical Research.

In the Indiana University School of Medicine, W. A. Brumfield has been appointed instructor in the department of bacteriology and pathology and Wemple Dodds promoted from instructor to assistant professor.

According to the *British Medical Journal*, the Nordhoff-Jung Cancer Prize for the best recent work on cancer has been awarded to Alexis Carrel, of the Rockefeller Institute for Medical Research, for his methods of tissue culture and its application to the problems of growth of tumors.

David Marine has received the gold medal of the New York Academy of Medicine for his investigations of the thyroid gland.

J. H. Teacher, St. Mungo (Notman) professor of pathology in Glasgow University, has died at the age of 61 years.

Major G. Seelig is directing the cancer program of the Barnard Free Skin and Cancer Hospital in St. Louis.

Undulant Fever—It is reported that the French Government has accepted an offer by the Rockefeller Foundation to establish a center for the study of undulant fever at Montpellier.

Bacterial Nomenclature—The International Society for Microbiology has taken up bacterial nomenclature as part of its permanent program. The matter has been placed in charge of a committee, of which R. S. Breed, New York Agricultural Experiment Station, Geneva, is one of the secretaries. The year of the publication of Linnaeus' *Species Plantarum*, namely, 1753, has been adopted as the date of departure for eventual international agreements in the naming of bacteria.

In Honor of James Ewing—The homage volume issued to commemorate his sixty-fourth birthday, was presented formally to James Ewing at a large dinner in his honor on Jan. 31, 1931.

Obituary

VERANUS ALVA MOORE

1859-1931

In the early morning of Feb 11, 1931, death claimed Dr Veranus A Moore, who, prior to his retirement in 1929, for thirty-three years had been professor of comparative pathology and bacteriology in the New York State Veterinary College at Cornell University, and for twenty-one years had served as its dean and director

Dean Moore's life was largely shaped by an accident which he suffered as a boy of 13 on his father's farm in Jefferson County, New York. He stepped on a nail, and an infection of the bone resulted which forced him to walk with crutches until he was 25 years old. Seeking aid for his affliction, the young man visited many physicians and hospitals and gradually became much interested in medicine. His disability was finally removed almost completely by an operation. After graduating from Cornell University with the B. S. degree in 1887, he pursued medical studies at Columbian University (now George Washington University) in Washington, D. C., and received his M. D. degree in 1890, while serving as an assistant in the pathological division of the Bureau of Animal Industry. In later years he received the degree V. M. D. from the University of Pennsylvania and that of D. Sc. from Syracuse University.

From 1890 to 1896, Doctor Moore was engaged in research in animal diseases with Dr Theobald Smith in the Bureau of Animal Industry at Washington, some of his first scientific work being on Texas fever, which then was being actively investigated. He later collaborated on the researches on hog cholera, and worked independently on the disease of chickens, now known as fowl typhoid. He succeeded in isolating and proving the relationship of the causative organism to the disease. During the last year before his return to Cornell, Doctor Moore became the chief of the pathological division, succeeding Theobald Smith in this office when the latter went to Harvard.

Returning to his alma mater in 1896 Doctor Moore became a member of the original faculty of the New York State Veterinary College. He took an active interest in the infectious diseases of the domestic animals and soon became known as one well versed in his profession. On the retirement of James Law, in 1908, he was chosen director of the college.

Quiet and unassuming always, but nevertheless firm when firmness was demanded, Dean Moore proved to be an able and inspiring teacher, a capable executive, a true friend to his colleagues, students and other friends, a devoted worker for his University and the city in which he lived, and a wise counsellor to his state and nation in matters relating to the health of animals, and in the protection of the livestock as well as the human family from those diseases that are carried by animals.

Dean Moore engaged in many activities outside of his university work. He served his city on many occasions, especially on the school and health boards. When the federal meat inspection act was passed, he was a member of the commission which drew up regulations under which the law was to function. During the World War, he served in civilian capacity as an advisor on the organization of the Army Veterinary Service. In recent years, he has served as an advisor on the Milbank Foundation, and on President Hoover's White House Conference on Child Health.

Dean Moore was the author of many scientific articles dealing with animal pathology and especially with bovine tuberculosis, on which he was recognized as an authority. He was the author of several books, the best known of which are his "Pathology and Differential Diagnosis of the Infectious Diseases of Animals" and "Bovine Tuberculosis and Its Control."

W A HAGAN

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

HIGH ELECTRICAL RESISTANCE OF THE SKIN OF NEW-BORN INFANTS AND ITS SIGNIFICANCE CURT P RICHTER, *Am J Dis Child* **40** 18, 1930

The resistance offered to the passage of a galvanic current through the body of a new-born infant is much greater than that in adults. The resistance of the skin on the backs of the hands (dorsal resistance), which is typical for the skin on the rest of the body, is very high. In some infants it is so high that the skin is almost completely impermeable. It was pointed out how this high dorsal resistance reflects a high degree of muscular relaxation in the infant. The resistance of the skin on the palms of the hands (palmar resistance) also is much higher than that which is found in adults. It was shown how the palmar resistance is correlated with the sleep of the infant, that is, the deeper the sleep the higher the palmar resistance. The general significance of these observations in the understanding of the physiology of the new-born infant was discussed. It was shown how the presence of an inhibition of the sympathetic and a possible dominance of the parasympathetic is indicated through the high palmar resistance in the new-born infant. It was pointed out that according to previous results the high dorsal and palmar resistance would indicate a very small amount of insensible perspiration and sweating in the new-born infant.

AUTHOR'S SUMMARY

THE PROBLEM OF DENTAL CARIES R W BUNTING and Others, *Am J Dis Child* **40** 536, 1930

In the study of the cause and control of dental caries there is need for a fuller understanding of basic facts concerning the disease which have already been established. Many theories have been advanced that are not in accord with known facts. Evidence is given in support of the view that dental caries is a specific infective process, the activity of which is dependent on certain metabolic states. As the result of dietary and therapeutic experiments, active dental caries was reduced to a negligible quantity in 433 children. Of the methods employed, dietary measures appeared to be the most important. The diets prescribed for the control of dental caries were well balanced, well fortified, adequate rations in which sugar was reduced to the minimum.

AUTHORS' SUMMARY

THE CORPUS LUTEUM AND THE MENSTRUAL CYCLE CARL G HARTMAN, *Am J Obst & Gynec* **19** 511, 1930

Menstrual bleeding is held to be foreshadowed and typified in the lower animals, especially the primate. A study in the *rhesus* monkey shows that ovulation is not essential for menstruation, which occurs without any sign of recent ovulation. Hence the corpus luteum is not the underlying factor in producing the rhythmic menses. The corpus luteum, on the other hand, is inevitably associated with premenstrual hypertrophy. The association appears to be one of cause and effect, although Hartman is loathe to conclude this. He proposes that the causative factor of menstruation be sought outside of the ovary, though it cooperates with this organ in maintaining the menstrual rhythm. It is suggested that the hemorrhages of menstruation and implantation be considered as homologous processes.

A J KOBAK

PLEURAL EFFUSIONS MAN PINNER and GEORGINE MOERKE, *Am Rev Tuberc* 22 121, 1930

Experiments on rabbits show that the normal pleura is highly permeable in either direction for the constituents of the blood. In patients with pleural effusions under pneumothorax treatment for pulmonary tuberculosis, a marked decrease of the pleural permeability is shown by actual experiments and must be assumed to exist from the results of chemical studies of the blood and the pleural effusion. Neither chemical, cytological, or serologic data afford, per se, dependable diagnostic or prognostic criteria. The failure of resorption of pleural effusion cannot be explained by the chemical constitution, it must be due to an alteration in pleural permeability.

H J CORPER

ADDISON'S DISEASE IN A NEGRO REPORT OF A CASE ANGELO M SALA and MENDEL JACOBI, *Arch Int Med* 46 375, 1930

The fifth case of Addison's disease in a Negro, with autopsy observations, is recorded in detail. The other recorded cases are reviewed. A comparison is made with the disease in white persons. The difficulty of diagnosis and the prominence of symptoms not usually stressed in white people are emphasized. The laryngeal and respiratory symptoms are stressed particularly.

AUTHORS' SUMMARY

THE REACTION OF THE CENTRAL NERVOUS SYSTEM TO EXPERIMENTAL UREA INTOXICATION BERNARD J ALPERS, *Arch Neurol & Psychiat* 24 492, 1930

Alpers investigated the reaction of the interstitial tissues of the brain of the rabbit to intoxications with urea. Changes were present in both gray and white substances, but especially in the latter. The microglia showed no, or a very mild, reaction (thickening and hypertrophy of the processes), in a severe case, fusiform or nodular swellings were scattered over the processes. The neuroglia, mainly the fibrous glia, was profoundly altered, especially around the blood vessels. It appeared as swollen and hypertrophied cell bodies with formation, in one severe case, of ameboid glia and clasmotodendrosis. In the former the nucleus was shrunk and more or less pyknotic, the processes were greatly swollen, the cytoplasm became granular and finally homogeneous. The vascular feet were disintegrated, they became greatly swollen, vacuolated, at first coarsely and later finely granular and shrank considerably. Changes were also exhibited by the macroglia cells described by Andriezen, and termed perivascular neuroglia by Hortega, many of which became pulverized and were represented only by remnants of a coarsely granular cytoplasm. Oligodendroglia (glia nuclei) showed changes only in severe cases—the nucleus was swollen and vacuolated, and the cytoplasm reticulated and also swollen. In contrast, the ganglion cells showed mild changes (reduplication of the nucleolus). Fat granule bodies did not occur in this case. The fact that the neuroglia cells in close proximity to the blood vessels were especially affected suggests a possible function of the neuroglia "to neutralize the effect of noxious agents circulating in the nervous system, and in this way to protect the nobler elements against harm."

G B HASSIN

EXPERIMENTAL LESIONS IN THE TUBER CINEREUM OF THE DOG L O MORGAN and C A JOHNSON, *Arch Neurol & Psychiat* 24 696, 1930

The authors succeeded in producing epileptiform seizures in dogs by injecting about 0.1 cc of a weak solution (from 0.2 to 0.5 per cent) of mercuric chloride into the tuber cinereum. As in real epilepsy, the convulsions occurred periodically, the animals otherwise remaining normal. The convulsions, which began from two to six hours after the operation, were mild, in the form of dilatation of the pupils, salivation, muscular spasms of the face, the jaws and, to a varied extent the anterior part of the body.

In a majority of cases the convulsions continued gradually to become severer and more frequent. The foregoing symptoms and signs were followed by rigidity, falling and general clonic convulsions of from one and a half to three minutes' duration. With the convulsive state over, the animal would remain unconscious for several minutes, then would be confused and disoriented. With the increase in frequency of the convulsions, the dog would pass into status epilepticus, and death was preceded by continuous coma, an increased rate of heart beats (from 230 to 260) and a rise of temperature (from 108 to 117 F). The time from the beginning of the first convulsion to the death of the animal was usually from ten to twenty hours.

A chemical analysis of the blood in the animals experimented on showed no changes in the calcium or potassium content of the serums, or any appreciable alteration in the potassium-calcium ratio. As the convulsions increased in frequency and severity, an inconstant increase of the nonprotein nitrogen and a decrease in the carbon dioxide combining power of the plasma resulted, while the sugar content of the blood first rose steadily to about twice the normal value and then sank steadily until the animal's death.

G B HASSIN

THE PERMEABILITY OF THE HEMATO-ENCEPHALIC BARRIER AS DETERMINED BY THE BROMIDE METHOD. SAMUEL T. GORDY and STEPHEN M. SMITH, *Arch Neurol & Psychiat* 24 727, 1930

In Gordy and Smith's studies of meningeal permeability, that is, the passing of chemical substances from the blood to the spinal fluid through the so-called hemato-encephalic barrier (the vascular endothelium in apposition with ependymal cells of the choroid plexus or with the meninges), they used the bromide method of Walter on 183 patients (108 men and 75 women). For deproteinization they utilized the nascent tungstic acid with the ordinary reagents used in the Folin-Wu system of analysis of the blood. The ordinary ratio between the bromide distribution in the blood and that in the spinal fluid—the permeability quotient—is about 3. This denotes that the concentration of bromide in the blood is three times stronger than that in the spinal fluid. In the majority of patients with dementia paralytica it was below 3, that is, it was increased. Some patients with schizophrenia showed a decreased permeability, about one half of them showed a normal permeability quotient, while some (24 per cent) showed an increased permeability. In the manic depressive patients about one half showed normal and the other half increased permeability. In cases of postencephalitis or senile psychosis, the conclusions were of no particular value, in patients with the alcoholic and arteriosclerotic types of psychosis there was a marked tendency toward increased permeability. The authors also concluded that with the Walter bromide method it was not possible to differentiate between dementia praecox and the manic-depressive psychosis, and that the deviations of permeability quotients from the normal, occurring in patients with some form of psychosis, denote them to be organic lesions of the brain.

G B HASSIN

PATHOGENESIS OF AMAUROTIC IDIOCY. CHARLES SCHAFER, *Arch Neurol & Psychiat* 24 765, 1930

From a study of a few portions of the brain and cerebellum of a case of Niemann-Pick's disease, Schaffer concludes that in contrast to amaurotic family idiocy (Tay-Sachs' type), which is an endogenous ectodermal disease, the former is a disease of the mesodermal layer. Both are constitutional, congenital and familial diseases, characterized by racial predisposition. On account of their endogenous basis they may occur simultaneously, as a combined disease of the germ layer (of the ectoderm and mesoderm), but they are essentially different morbid entities. They also show some histologic differences. In Niemann-Pick's disease the cell expansion is far less pronounced than in Tay-Sachs' disease, and a fine prelipoid granulation is present only in the Purkinje cells, while in

Tay-Sachs' disease it is found in all of the cerebellar neurons, in Niemann-Pick's disease the fat-storing cells appear in the nerve parenchyma as prelipoid bodies, and a fine granulation with lipid substances is present in the mesodermal tissues—the leptomeninges and the blood vessels. In Tay-Sachs' disease the fat-storing cells and the fine granulations are absent.

G. B. HASSIN

EXPERIMENTAL FIBROUS OSTEODYSTROPHY (OSTITIS FIBROSA) IN HYPERPARATHYROID DOGS. H. L. JAFFE and A. BODANSKY, *J. Exper. Med.* **52** 669, 1930.

These experiments have shown that parathyroid extract (parathormone Collip) can be injected into puppies in increasing amounts for long periods without fatal results. Thus time is allowed for bone changes to develop. Long continued injection leads to progressive decalcification and resorption of the existing bone, to fibrous replacement of the marrow and to the production of the other features characteristic of *ostitis fibrosa*. Deformities eventually appear. It is safe to assume that the changes in the bone produced by hyperparathyroidization have the same pathogenesis as those observed in clinical cases believed to be instances of hyperparathyroidism—that is, cases with a negative mineral balance and decalcification of the skeleton.

AUTHORS' SUMMARY

EFFECT OF SIZE OF EXPLANT ON CULTURES OF FIBROBLASTS. W. R. EARLE and J. W. THOMPSON, *Pub. Health Rep.* **45** 2672, 1930.

An attempt was made to study the influence of the size of the explant on cultures of fibroblasts of the chick, planted in a small, thin hanging drop of embryo juice and plasma. This medium was not changed during the life of the culture. The explants used varied from only a few cells to cell clumps about 1 mm. cube in volume. Fibroblasts from fresh chick heart and from a stock strain were used.

It was found that for the cultures studied, the absolute increase in the area of a culture varied approximately directly as the size of the explant.

Further, the final maximal size of a culture also varied approximately directly as the size of the explant, and in cultures from the smallest explants it was very slight indeed.

MOTTLED ENAMEL IN A SEGREGATED POPULATION. G. A. KEMPF and F. S. MCKAY, *Pub. Health Rep.* **45** 2923, 1930.

At the present time no definite conclusions about the cause of mottled teeth can be drawn. From observations made over a period of years, the dystrophy of the enamel seems to occur in certain areas in the United States, and the etiologic factors seem to be definitely associated with the water supply. A child exposed during the period of growth of the permanent enamel to the environmental factors of an endemic area is almost certain to develop mottled enamel of the teeth. An excellent bibliography of reports on this disease covering the past thirty years is included at the end of this paper.

THE INTRAOCULAR PRESSURE AND DRAINAGE OF THE AQUEOUS HUMOUR. FREDERICK RIDLEY, *Brit. J. Exper. Path.* **11** 217, 1930.

The cornea is a normal and constant path of drainage of the aqueous humor. Drainage takes place chiefly via the filtration angle. The corneal path of drainage is probably the only one by which aqueous humor is normally and constantly removed. The sclera is not indistensible. Curves of distensibility are described, and their significance is discussed. The influence of expansion of the vascular

bed of the uvea on the intra-ocular pressure is demonstrated. A mechanism is described by which the intra-ocular pressure may be attained, maintained and varied. The manner in which failure of drainage may give rise to increased intra-ocular pressure is described. In a theoretical summary the conditions controlling the intra-ocular pressure and aqueous drainage are correlated, and their application to the problem of glaucoma is indicated.

AUTHOR'S SUMMARY

THE PHARMACOLOGICAL ACTION OF THE EXOTOXIN OF STAPHYLOCOCCUS AUREUS. C. H. KELLAWAY, F. M. BURNET and F. ELEANOR WILLIAMS, *J. Path. & Bact.* **33** 889, 1930.

The intravenous injection of crude agar staphylococcal toxin into the cat and rabbit has a two-fold effect on the blood pressure. There is first a transient fall with recovery above normal, and secondly a rapid terminal fall. The initial transient fall is vasomotor in origin and is due to the presence in the toxin of pharmacologically active constituents of the media. After this initial fall the excessive rise during recovery is possibly contributed to by an increased output of epinephrine. In confirmation of the contention of Russ, the final fall in the blood pressure is shown to be due principally to obstruction of the pulmonary circulation. That there is a direct action on the heart which is contributory to the failure of the right side of the heart following obstruction is shown by the use of the isolated heart with an artificial pulmonary as well as an artificial systemic circulation. These phenomena attending the final fall of blood pressure do not occur in the immune animal, or in animals passively protected by antitoxin. The absence of complete protection by overneutralization with antitoxin is discussed, and the artificial nature of a test by intravenous injection is insisted on, since the toxin under these conditions reaches the heart and lungs in high concentration directly following the injection.

AUTHORS' SUMMARY

ENCEPHALITIS PERIARIALIS DIFFUSA IN A RHESUS MONKEY. J. R. PERDRAU, *J. Path. & Bact.* **33** 991, 1930.

The knowledge that Schilder's encephalitis occurs naturally in the rhesus monkey demands the exercise of great care that the natural disease is not mistaken for the experimental one when attempts are made to reproduce one of the human demyelinating diseases in this species of monkey. At the same time the rhesus is valuable as a susceptible animal for this particular type of encephalitis.

AUTHOR'S SUMMARY

LIVER EXTRACT IN EXPERIMENTAL ANAEMIAS. G. PAULING WRIGHT and BARBARA ARTHUR, *J. Path. & Bact.* **33** 1017, 1930.

The administration of an extract of liver, effective in the treatment of pernicious anemia, has no significant influence on the red cell or the reticulocyte counts of normal rabbits. The regeneration from anemia resulting from the injection of phenylhydrazine or from hemorrhage is not affected by the administration of the substance effective in pernicious anemia. Measurements of the diameters of the red cells together with the differences in the severity of the anemia indicate that the administration of liver extract mitigates the severity of the anemia produced by phenylhydrazine. This phenomenon is probably in no way concerned with the activity of the extract in the treatment of pernicious anemia. The administration of liver extract results in a diminution in the size of the polychromatic cells liberated from the marrow. It is suggested that liver extract acts in pernicious anemia by promoting the due degeneration of the megaloblastic phase of erythropoiesis.

AUTHORS' SUMMARY

EXCRETION OF URINARY PIGMENT LUDWIG HEILMEYER, Ztschr f d ges exper Med **72** 545, 1930

The excretion of urinary pigment was determined in twelve cases of exophthalmic goiter. In three cases it was higher than normal. In each of these three cases there were signs of thyrotoxic circulatory failure. No association was noted between the amount of urinary pigment and increased metabolism. One case with a basal metabolism of +130 per cent showed no increase in urinary pigment as long as the circulation remained normal. Also, no change in the excretion of pigment was noted following therapeutic doses of thyroxine and thyroid gland. These observations tend to contradict the hypothesis of Dabkin, that a relationship exists between increased metabolism and the excretion of urinary pigment.

PEARL ZEEK

VASONEUROTIC DIATHESIS KARL A. BOCK, Ztschr f d ges exper Med **72** 561, 1930

Investigations were made in regard to a group of diseases in which there were disturbances in the "vegetative-endocrine-electrolytic milieu." Certain cases of gastric and duodenal ulcer were included. In such cases long administration of thyroxine and of certain preparations of vitamins readily caused changes in form and function to appear in the capillary system, as viewed on photographic plates. Such changes did not appear in normal controls. In diseases associated with constitutional hypertension this reaction occurred very early in the disease, while the blood pressure was still relatively low and fluctuating. As blood pressure climbed higher and hypertension became permanent, the reaction disappeared. In persons of this diathesis the action of epinephrine was reduced, as compared with that in healthy persons, but after thyroid treatment it approached the normal. Also, in these persons, there was greater acidity of the tissues, but this factor may have been influenced by the diet. The increased acidity of the tissues might account for the type of reactions to epinephrine and thyroxine obtained in these persons, since the activity of these hormones is influenced by the degree of acidity of the tissues.

PEARL ZEEK

ALTERATIONS IN LEUKOCYTES IN VITRO HORATIO GOLDIE, Ztschr f d ges exper Med **72** 637, 1930

Two groups of changes in leukocytes are described, necrobiosis and metamorphosis. The former is an expression of loss of vitality and disintegration of structure. The latter includes cellular hypertrophy, division and autolysis and represents acceleration of cellular processes. It may be brought about by various irritative factors.

PEARL ZEEK

THE VITAL IMPREGNATION OF THE AORTIC WALL WITH TRYPAN BLUE W. HACKEL, Ztschr f d ges exper Med **72** 762, 1930

Experiments revealed that impregnation of the aortic wall with dyestuffs was more marked in animals with artificially increased blood pressure, than in those with normal blood pressure. The site of greatest infiltration seemed to be the same as that in which lipoidal degeneration is commonly found. The same applied to infiltration of the semilunar cusps of the aortic valve.

PEARL, ZEEK

EXPERIMENTS ON THE PATHOGENESIS OF ASEPTIC AND ATRAUMATIC PLEURITIS T. KANAI and K. MINAMI, Ztschr f Tuberk **56** 434, 1930

Exudative pleuritis occurs in about fourteen per thousand of all Japanese soldiers. It is very doubtful whether this pleuritis is tuberculous, since it is

much more frequent in the Japanese army than in Western armies, while the mortality from tuberculosis in Japan is essentially the same as that in Western countries. Experimentally it was shown that the intravenous injection of sympathicotonic drugs with forced bodily movements caused large pleural effusions. Parasympathicotonic drugs exert no such influences, and they even prevent the action of the former class of drugs. It is concluded that Japanese "military pleuritis" is caused by strictly metabolic and nervous disorders, due to the sudden change in living conditions.

MAX PINNER

Pathologic Anatomy

THE CORONARY ARTERIES OF THE DOG ROBERT A. MOORE, *Am Heart J* 5 743, 1930

The coronary arteries of the dog differ from those of man in two major points: the presence of a distinct and separate septal artery as a branch of the left coronary artery, and the formation of the posterior descending artery by the left in all cases rather than in 20 per cent as in man. The origin and course of the septal artery render experimental ligation of it difficult. It is improbable that previous investigators have interrupted the blood supply to the septum. Anastomoses between the coronary arteries and their branches are extremely abundant in the dog's heart.

AUTHOR'S SUMMARY

POLYPOID FIBROMA OF THE LEFT AURICLE (SO-CALLED CARDIAC MYXOMA) CAUSING A BALL-VALVE ACTION G. H. HOUCK and G. A. BENNETT, *Am Heart J* 5 787, 1930

A case of intracardiac tumor arising from the interauricular septum is reported and illustrated by gross and microscopic photographs. We have found no record of this condition ever having been diagnosed before necropsy. A tumor of this type may produce a ball-valve action in every way similar to the action of a ball thrombus.

AUTHORS' SUMMARY

ANEURYSMS OF THE BRONCHIAL ARTERIES MENDEL JACOBI, *Am Heart J* 5 795, 1930

A case of multiple, saccular aneurysm of the bronchial arteries is reported, the first recorded in the literature. Death resulted from asphyxia caused by tracheal occlusion by the aneurysm. The etiology is shown definitely to be syphilitic, a rather unusual observation in aneurysms of smaller arteries. Many other small and several medium-sized arteries showed syphilitic involvement varying from the early lesions of endarteritis of the vasa vasorum and lymphocytic perivascular infiltration of the adventitia to extensive destruction of the elastic lamellae. The role of the supporting external structures in the formation of the aneurysms of the intercostal arteries and aorta in this case is indicated.

AUTHOR'S SUMMARY

OSTEITIS FIBROSA CYSTICA GENERALIZED TYPE WITH GIANT CELL SARCOMA BENJAMIN M. JOSEPH, *Am J Dis Child* 40 81, 1930

Microscopic sections of biopsy material showed giant cell sarcoma in an inguinal lymph node from a patient with generalized osteitis fibrosa cystica.

P. H. GUINAND

CONGENITAL PNEUMOTHORAX JACOB STEIN, *Am J Dis Child* **40** 89, 1930

A case of congenital pneumothorax is described. A thorough review of the literature in all languages indexed at the New York medical libraries disclosed reports of only four cases previous to this one.

AUTHOR'S SUMMARY

GIANT CELLS IN INFLAMMATIONS OF THE LUNG IN CHILDREN ROBERT A. MOORE and PAUL GROSS, *Am J Dis Child* **40** 247, 1930

At least four types of multinucleated cells are found in inflammations of the lung in children. Multinucleated cells may be formed by fusion of degenerated exudate, desquamated bronchial epithelium and desquamated alveolar epithelium. There is no evidence that pneumonia associated with multinucleated cells constitutes a distinct type. Extensive desquamation and giant cell formation may occur independent of alveolar exudation and may be either a distinct type of alterative inflammation of the lung or a part of the pathologic changes of pneumonia alba. Giant cells in association with pneumonia have no specific cause.

AUTHORS' SUMMARY

NEPHROSCLEROSIS (CHRONIC INTERSTITIAL NEPHRITIS) IN CHILDHOOD A. GRAEME MITCHELL, *Am J Dis Child* **40** 345, 1930

A comprehensive review of the subject of nephrosclerosis in children with special reference to renal rickets is presented. In his summary the author states that in studying the literature on nephrosclerosis, it is found that the terminology is confusing. The term chronic interstitial nephritis, which has been employed for a long time to describe the essential underlying pathologic process, is more descriptive of an end-result than of a definite entity. It is suggested that for the use of the clinician a simple terminology be adopted somewhat as follows: acute hemorrhage (glomerular) nephritis, acute edematous (tubular) nephritis (sometimes called nephrosis), chronic nephritis which is usually diffuse, but in which glomeruli, tubules, blood vessels or interstitial tissue may be involved to a greater extent than in the remainder of the kidney structure, suppurative nephritis which may be acute or chronic, lipid nephrosis. It would seem that all cases of actual disease of the kidney could be grouped etiologically, pathologically and symptomatically under such a classification. The term nephrosis, and especially lipid nephrosis, should be reserved for a relatively small number of cases in which there have been determined such well defined criteria as changes in the albumin-globulin ratio of the blood, increase in blood cholesterol and the demonstration of doubly refractile lipid bodies in the urine. Two cases of renal rickets and four cases of chronic nephritis in children are reported.

P. H. GUINAND

CONGENITAL ATRESIA OF THE BILE DUCTS A. MATHIESON and I. HARRISON TUMPEER, *Am J Dis Child* **40** 571, 1930

Congenital atresia of the bile ducts is one form of hepatic anomaly frequently encountered in earliest infancy. The symptoms are those of complete obstruction of the bile passages. The prognosis is bad in cases of complete atresia. When a diagnosis of complete biliary obstruction has been established, exploratory operation should be performed with the hope that the anomaly of the bile passages may be of such a nature that a communication with the intestines may be effected. A case of complete biliary atresia not amenable to surgical correction is here described.

AUTHORS' SUMMARY

THE ORIGIN OF THE FIBROUS TISSUE ARISING IN THE TESTIS OF THE GUINEA PIG FOLLOWING EXPERIMENTAL TUBERCULOSIS GEORGE A BAITSSELL and KARL E MASON, *Am Rev Tubere* **21** 593, 1930

Infection of the testicular tissues of the guinea-pig with tubercle bacilli causes rapid and marked degenerative changes of the germinal cells in the seminiferous tubules. The onset of these changes is more rapid in the testes of the reinfected animals than it is in the controls. The degeneration of the germinal cells is followed by their rapid elimination from the testes, which results in a marked decrease in the diameter of the tubules and a corresponding increase in the size of the intertubular areas. The rapid formation of an abundant exudate in the enlarged intertubular areas is a prominent feature of the histologic changes. The formation of fibrous tissue is brought about as the result of a direct transformation of the elements of the exudate in the intertubular areas. In the first stage there is a fine fibrillation with a typical appearance of a reticulum in the more advanced stage. The climax is reached in the formation of heavy bundles of wavy fibers identical with and staining for collagenous fibers. These fibers infiltrate and encapsulate the developing tubercles and, in general, permeate throughout the infected areas. The entire process of fibrous tissue formation is due to the fusion and consolidation of the minute filaments present in the exudate. This does not preclude the possibility that the infiltrating cells may alter the chemical nature of the developing fibrous tissue by means of cellular secretions, or the possibility that the movements of the cells through the exudate may, through mechanical factors, aid in bringing about the fusion of the fibrin-like elements present in the exudate. The development of the tubercles, which are characteristic of tissues infected with tubercle bacilli, in the infected regions of the testes takes place in the greatly enlarged intertubular areas following the exudate formation, cellular infiltration and development of the fibrous tissues. H J CORPER

PYLORIC OCCLUSION FROM SULPHURIC ACID H A BRUCE, *Ann Surg* **92** 897, 1930

Complete pyloric inflammatory occlusion for a distance of 3 inches (7.6 cm) resulted from the ingestion of 3 ounces (89 cc) of sulphuric acid. Nine weeks after the accident, gastro-enterostomy showed a narrowed first and second portion of the duodenum. The dilated stomach showed only small hemorrhagic or fibrotic areas. The lips, mouth, pharynx and esophagus escaped serious damage. As is usual, in most cases the pyloric end of the stomach suffered most of the pathologic changes.

RICHARD A LIFVENDAHL

THE LIFE OF RETICULOCYTES CLARK W HEATH and GENEVA A DALAND, *Arch Int Med* **46** 533, 1930

Reticulocytes in vitro at 37 C and in the pleural cavity of the rabbit decrease at a regular rate over a period of from one to four days. This rate is analogous to a death rate or a maturation rate. The rate is similar for reticulocytes from various sources, for example, from bled rabbits, from those into which phenylhydrazine is injected and from cases of hemolytic jaundice and pernicious anemia. The rate is much slower at 23 C or at 10 C than at 37 C. Reticulocytes have been found in blood kept in the icebox for six months. The decrease in the number of reticulocytes is not related to degenerative changes which may take place in the blood in vitro. No dependable conclusion regarding the maturation rate of reticulocytes can be drawn from the experiments on the transfusion of reticulocytes into rabbits, but the results are not inconsistent with the observations concerning their decrease in the test tube. As the reticulocytes decrease in number in vitro, cells with "granules" progressively increase. Reticulocytes having large amounts of reticular substance are less mature than those having small amounts of reticular substance and require a longer period of time to reach maturity. There is an undoubted analogy between the rate of decrease in the

number of reticulocytes in vitro and of those in the blood stream. In both instances this is probably true maturation. Evidence strongly in favor of this conclusion is given by studies on reticulocytes from the blood of patients with pernicious anemia during the reticulocyte responses following liver therapy.

AUTHORS' SUMMARY

MYATONIA CONGENITA WITH PARTICULAR REFERENCE TO PATHOLOGY AND FAMILIAL TENDENCY E. S. GURDJIAN, Arch Neurol & Psychiat **24** 52, 1930

Of four patients with myatonia congenita (amyotonia or Oppenheim's disease) studied, one, a child aged 2½ years, died of bronchopneumonia. There were a paucity of ganglion cells in the anterior horns of the spinal cord, swelling with dislocation of the nuclei to the periphery and, in many cells, a lack of Nissl bodies. These changes were especially marked in the dorsolumbar region and were present also in Clarke's column. The anterior roots, especially of the lumbar region and the cauda equina, were atrophied and poor in myelin substance. The muscles—gastrocnemius and iliopsoas—also appeared atrophied and pale, the "interstitial nuclei" were increased, with perivascular infiltrations of lymphocytes and plasma cells. The heart showed subendocardial, fatty, degenerative infiltration, and lymphocytes and plasma cells were present in the "subserous material." The rest of the organs showed no noteworthy changes. Gurdjian concludes that myatonia congenita is akin to the Werdnig-Hoffmann type of muscular atrophy but is a less advanced stage of a lesion of the central and peripheral nervous systems, and that it may occur long after birth and be due to an infection or intoxication of the neuromuscular system (anterior horn cells, anterior nerve roots and striated muscle).

G. B. HASSIN

NIEMANN-PICK'S DISEASE GEORGE B. HASSIN, Arch Neurol & Psychiat **24** 61, 1930

The macroscopic and microscopic changes in a case of Niemann-Pick's disease much resembled those seen in the infantile type of amaurotic family idiocy (Tay-Sachs' disease), the brain was hard and leathery to the touch, the sylvian and interparietal fissures were gaping, and the frontal convolutions were markedly atrophied, the corpus callosum was thin, the ganglion cells appeared large and honeycombed, their nuclei were peripherally located and the apical dendron, like the cell body, was swollen. Few Nissl bodies were present in the expanded cell body, where they gathered around the nucleus. In some areas, the optic thalamus, for instance, these bodies were lacking. The contents of the cell body, its reticular cytoplasm, stained dark with any hematoxylin method and pale orange with scarlet red and appeared dustlike when stained with the silver method of Bielschowsky or Schultze-Stohr. Other cells, also honeycombed but without processes, stained bright red with scarlet red, and these fat granule bodies were especially gathered around the blood vessels. Neurofibrils were few and were always pushed to the periphery. The same type of changes were seen in the cerebellum. The Purkinje cells were practically absent or greatly changed and were for the most part replaced by so-called "foam" cells and dense glia fibers. The optic thalamus was also markedly changed and like the cerebellum was transformed into a glia tissue scar. The "foam" cells, so typical of Niemann-Pick's disease, were also present in the arachnoid membrane, the ependyma of the sylvian aqueduct and the pineal body, and resembled the "foam" cells which were found in the rest of the body (liver, kidney, spleen, etc.). The changes in this condition are more advanced than those in amaurotic family idiocy (Tay-Sachs' type), and with the latter belong to a group of some metabolic disorder. However, it is hardly the same disease, for visceral changes described in Niemann-Pick's disease do not occur in amaurotic family idiocy, nor do all cases of Niemann-Pick's disease exhibit cerebral changes typical of amaurotic family idiocy.

AUTHOR'S ABSTRACT

HYALINE DEGENERATION IN DEMENTIA PARALYTICA ABNER WOLF, Arch Neurol & Psychiat **24** 71, 1930

In a patient, aged 48, who died of dementia paralytica, the frontal lobe exhibited a somewhat softened area, 2 cm in diameter and extending 3 cm deep, in the upper portion of the left precentral gyrus. The affected area consisted of a glassy material of almost "cartilaginous toughness", smaller areas of similar structure occupied the occipital lobes, the second left temporal gyrus, both gyri recti and the thalamus. The rest of the tissues exhibited changes typical of dementia paralytica. The colloid mass appeared granular and argentophilic and, when stained with the various methods, proved to be a hyaline and carminophile substance. Many blood vessels showed a beginning deposit of hyalin in their walls, while other vessels were free or showed extensive and intensive hyalinization. Such areas exhibited large homogeneous macroglia cells and permitted study of the evolution of the process of hyalinization of the cortex, the various stages of the deposits of hyalin, the reaction of the surrounding tissues and the ultimate fate of the cerebral parenchyma. The conclusions Wolf arrived at are that in dementia paralytica disturbance of protein metabolism occurs, the walls of the vessels form the first barrier, being the first site of deposition of the abnormal material, the second defense mechanism is a ring of inflammation and reaction of macroglia, when the latter becomes insufficient, hyalin is precipitated, this results in destruction of the nervous parenchyma and formation of a status spongiosus (as a result of absorption of the deposits of hyalin).

G B HASSIN

SUBARACHNOID HEMORRHAGE AS A CLINICAL COMPLICATION OF NEURO-SYPHILIS IRVING J SANDS, Arch Neurol & Psychiat **24** 85, 1930

Hemorrhages in the brain or cerebral meninges are rarely encountered in neurosyphilis. Endarteritis or meningitis is more common. In one of the two cases reported of headache, pain in the occiput, drowsiness or unconsciousness with blurring of disks and bloody spinal fluid, a hemorrhage was found at the base of the brain, in the middle and posterior fossae. It surrounded the midbrain, pons, medulla and cerebellum. On the vertex of the brain, the pia-arachnoid showed extensive bloody infiltrations over the frontal and parietal areas. The fourth ventricle and some portions of the subarachnoid space were filled with blood. There was pial syphilitic endarteritis, and the cortical vessels were infiltrated with lymphocytes and plasma cells. The parenchymatous changes were mild, though the glial reaction in the cortex was intense. No hemorrhages were found within the brain substance proper. Sands concluded from his study that subarachnoid hemorrhages occurring in neurosyphilis are probably caused by rupture of diseased blood vessels of the pia.

G B HASSIN

CHANGES OF THE SPINAL CORD IN HODGKIN'S DISEASE PHILIP T SHAPIRO, Arch Neurol & Psychiat **24** 509, 1930

The changes in the spinal cord in two cases of Hodgkin's disease are described. In the first, that of a colored woman, aged 32, with flaccid paralysis, there was an extensive infiltration of the spinal dura and the posterior nerve roots, with degenerative changes in the adjacent cord. In the second case also in a woman, aged 30, there was a flaccid paralysis of the lower extremities with changes in the spinal cord somewhat similar to those in subacute combined cord degenerations.

G B HASSIN

HUMAN BITE INFECTIONS OF THE HAND M L MASON and S L KOCII, Surg Gynec & Obst **51** 591, 1930

Infection of the dorsal surface of the hand and phalanges as the result of teeth penetrating the skin and underlying structures causes a definite clinical and pathologic picture. In most cases the infection is of a mixed type from the onset,

although the fusiform spirillum is frequently found and is accountable in part for the foul-smelling and gangrenous lesions that so frequently occur. Recurrent "flare-ups" of the infection after incision are attributed to anaerobic organisms which reach sufficient growth in from four to five weeks to produce symptoms. Experimental injections demonstrate that the infection is likely to extend (1) lateralward in the subcutaneous tissues, (2) under the digital fascia of the proximal phalanx and around the finger, (3) more deeply, distalward along the proximal phalanx under the extensor tendon, with subsequent periosteitis and osteomyelitis, (4) under the extensor tendons and fibrous tissue, (5) into the middle palmar or thenar space by way of the lumbrical canal, (6) through the joint into the palm, under the volar interosseous fascia and then into the middle palmar or thenar space, and (7) into the synovial sheath and flexor tendons by erosion of the fibrous flexor tendon sheath.

RICHARD A. LIVVENDAHL

EFFECTS OF THE ELECTROCAUTERY ON NORMAL TISSUES. J. GOTTFESMAN, D. PERLA and J. M. ZIGLER, *Surg Gynec & Obst* **51** 667, 1930

A comparative study of the manner and rate of repair of incisions aseptically produced by scalpel and those by desiccating knife of the electrocautery is reported. It was found that the latter produces extensive necrosis which acts as a foreign body with a resulting foreign body giant cell reaction in the skin, muscle, liver, kidney and spleen. These wounds heal more slowly and tend to suppurate more frequently than those made by the scalpel. It is also suggested that in cases of malignant tumors, cauterization seals the lymphatics, but that subsequent absorption is not decreased, because the lymph channels rapidly regenerate in granulation tissue. Secondary hemorrhage is also an inherent danger.

RICHARD A. LIVVENDAHL

THE PATHOLOGICAL CHANGES FOUND IN A FATAL CASE OF PSITTACOSIS. G. HASWELL WILSON, *J Path & Bact* **33** 957, 1930

The general picture is that of septicemia accompanied by distinctive changes in the lungs. These are, in the order of their occurrence, congestion with abundant serous exudation, which ultimately becomes fibrinous, degeneration and desquamation of the epithelium lining the air vesicles and bronchi, thrombosis of the capillaries, or actual necrosis of the walls of the air vesicles in areas in which the damage is more severe, with hemorrhage in places. A relative absence of polymorphonuclear leukocytes is a striking feature and is consistent with the leukopenia observed clinically and with the microscopic appearances of the bone marrow.

FROM AUTHOR'S SUMMARY

PERSISTENT EOSINOPHILIA. A. M. DRENNAN and J. H. BIGGART, *J Path & Bact* **33** 995, 1930

A case of persistent eosinophilia with splenomegaly and massive infiltration of the iliopsoas muscles is described. A suggestion is made that the syndrome "persistent eosinophilia and splenomegaly" may possibly be a functional disease—an expression of an excessive response on the part of the eosinophil to some as yet unidentified irritant.

AUTHORS' SUMMARY

NECROTIC SEQUESTRATION OF THE KIDNEYS IN PREGNANCY. WALTER DE M. SCRIVER and HORST OERTEL, *J Path & Bact* **33** 1071, 1930

Necrotic sequestration of the kidney in pregnancy is the result of a terminal arterial segmentary collapse (vasoparalysis) with blood stasis and segmentary thrombosis with proximal extensions. The sequestered areas are immediately

surrounded by vessels still in "prestasis" and further on in "peristasis." These renal vascular disturbances seem to be related to a general abnormal state of vasomotor irritability of the pregnant state (hypertension) which provincially is functionally and anatomically revealed in the skin and in parenchymatous organs, notably the brain, liver and kidneys (edema, exudation, hemorrhages and necrosis). Based on these and similar anatomic observations elsewhere (uremic ulcers, eclamptic livers and lesions of the spleen and brain) and on experimental evidence as regards irritative circulatory changes in the living warm-blooded animal, it seems that the assumption of a paralytic terminal segmentary circulatory downfall (peristasis, prestasis, stasis) is in better harmony with these observations than the idea of vascular spasm and ischemia. Moreover, it furnishes a more definite mechanical conception of these lesions than the various rather hazy theories of primary "toxic cell degenerations." The very high intravascular fat contents of some of these cases suggest an associated hyperlipemia. It appears from the records of other published cases that a similar circulatory collapse with thrombosis may occur in certain infectious diseases for similar reasons.

AUTHORS' SUMMARY

COAL-MINER'S LUNG S. LUTJ CUMMINS and A. F. SHADDEN, J. Path. & Bact. **33** 1095, 1930

The black material in anthracotic lungs consists chiefly of coal dust. Iron is not an important constituent. Silica is found in anthracotic lungs in abnormal amounts. The pathologic effect of silica is to damage and block the lymph channels, so impairing the normal power of the lungs to dispose of inhaled dust. Whenever coal dust is retained in large amounts there is found also a high silica content in the lungs. Anthracosis of the lungs is determined by a combination of silicotic fibrosis and accumulation of coal dust. A considerable degree of anthracosis is consistent with working health. Coal miners especially exposed to silica dust are liable to develop a silicosis which, complicated by the effects of accumulation of anthracotic dust, may lead to disablement and death.

AUTHORS' SUMMARY

CHANGES IN THE HEAD OF THE FEMUR IN SENILE DYSPLASIA OF THE HIP R. DE JONG, Virchows Arch. f. path. Anat. **275** 348, 1930

The condition to which the author devotes his attention develops slowly, without fever or disturbance of the general health, in the later years of life and leads to pain on and difficulty in walking. It is usually unilateral. It may begin at 32 to 35 years of age. It has been considered by some a form of arthritis deformans, although the proliferative reaction of the latter disease is absent. By some pathologists it has been termed chronic dry ulcerative arthritis of the hip. Jansen, on whose views the author draws freely, held the primary factor to be congenital flattening of the acetabulum. Jansen treats the condition by resection of the head of the femur. It is the femoral heads of six patients operated on by Jansen that de Jong describes in detail. The head is shorter and flatter than normal, and is more oval than round in shape. The free margin of the head is much more prominent than normal, and overrides the neck like a roof; it is this prominence of the margin that interferes with the gait. The round ligament is absent or atrophic. The cartilage of the convex portion of the head is eroded, and the exposed bone is hard and polished. On microscopic examination, the superficial lamellae and trabeculae of the bone of the femoral head were found to be denser than normal, compressed and closely applied to each other. There was no evidence of active resorption of bone by osteoclasts. The process is a degenerative and atrophic one. The deformity of the head of the femur results from pressure on bone the plasticity of which causes the bone to yield to the pressure. Concerning changes in the acetabulum or earlier stages of the process in the head of the femur, the author can express no opinion.

O. T. SCHULTZ

PROGRESSIVE DESTRUCTION OF VERTEBRAE M B SCHMIDT, *Virchows Arch f path Anat* **275** 373, 1930

Schmidt describes an unusual condition of progressive destruction of the vertebral bodies, which he ascribes to trauma, and which may therefore be of considerable medicolegal interest. The patient was a man, aged 32, who had complained of pain in the back for two years previous to his death. The final clinical diagnosis, based in part on roentgenographic evidence, was compression myelitis due to multiple tumor metastases of the vertebral column. At necropsy it was found that the tenth dorsal vertebra had disappeared, and that the eleventh vertebra had been reduced to a thin, wedge-shaped structure. The third, seventh, ninth and twelfth dorsal vertebrae revealed distortion of the end-plates of the vertebral bodies, swelling and slight laceration of the intervertebral disks and microscopic changes that Schmidt believes explain the more severe involvement of the tenth and eleventh vertebrae. The end-plates of the twelfth vertebra were partly broken and displaced into the spongy bone of the body of the vertebra. Small islands of cartilage were present in the bone beneath the end-plates. Such a misplacement of cartilage, which Schmorl has described as of frequent occurrence in apparently normal persons, the latter author has ascribed to the mechanical trauma of ordinary locomotion. The trabeculae of the spongy bone at the center of the twelfth vertebra were fractured, necrotic and in the process of resorption. There were hemorrhage and connective tissue reaction in this portion of the vertebral body. According to Schmidt, the disintegration, necrosis and resorption of spongy bone, once initiated, became a continuing process, which led to the complete disappearance of a vertebral body. The process described by Schmidt is unlike the progressive atrophy of vertebral bodies discussed by Schmorl and others. It has a striking similarity to the posttraumatic vertebral disease of Kummell. In the latter, however, the destructive process is limited to a single vertebral body, and there is usually a history of trauma, which is less severe than that required to cause a true vertebral fracture. In Schmidt's case no history of trauma to the spine could be elicited, but the author believes the lesion to have been the result of a mechanical trauma of so slight a grade that it escaped the patient's attention.

O T SCHULTZ

LIPOIDAL AND OXIDASE GRANULES IN THE LEUKOCYTES OF THE PERIPHERAL BLOOD W S NESTEROW, *Ztschr f d ges exper Med* **72** 256, 1930

Methods are described by which two varieties of monocytes may be recognized in the peripheral blood. They have different biologic functions and different staining reactions. One type, which in function seems to be related to reticulo-endothelium, takes up fragments of neutrophils, erythrocytes and lymphocytes, and does not contain lipid granules. These cells are not found normally in the peripheral blood. The second type is present in normal blood of human beings and dogs and contains lipidal and oxidase granules. In certain pathologic conditions the granules are increased in number.

PFARL ZEEK

SPONTANEOUS PNEUMOTHORAX CAUSED BY LYMPHOCYCLIC GRANULOMA R I KOTTLER, *Ztschr f Tuberk* **58** 37, 1930

A woman 23 years old showed at necropsy mediastinal and pulmonary lymphogranuloma, a spontaneous pneumothorax and a rupture into the esophagus, produced by specific lesions.

MAX PINNER

Microbiology and Parasitology

ACUTE SUPPURATIVE THYROIDITIS IN CHILDREN J M MORA, Am J Dis Child 40 500, 1930

Two unusual cases of acute suppurative thyroiditis in children, aged $2\frac{1}{2}$ and 13 years, respectively, with operative recovery, are recorded. In both cases the primary infection was a sore throat, and in both instances the offending organism was a hemolytic streptococcus.

AUTHOR'S SUMMARY

NITRITE REACTION AS A DIAGNOSTIC TEST IN INFLUENZAL MENINGITIS ROY M GREENTHAL, Am J Dis Child 40 569, 1930

A positive nitrite reaction with the spinal fluid was obtained in thirteen consecutive cases of influenzal meningitis, and was always absent in meningococcic, tuberculous and streptococcic meningitis. The nitrite test, according to the method described, may be used as a rapid corroborative test for the diagnosis of influenzal meningitis.

AUTHOR'S SUMMARY

INFECTIOUS MONONUCLEOSIS J P PRICE, Am J Dis Child 40 581, 1930

A case of infectious mononucleosis in a baby, aged 7 months, is reported with a general discussion of the disease. Especial reference is made to the difficulty in diagnosis between infectious mononucleosis and acute lymphatic leukemia in the early stage.

AUTHOR'S SUMMARY

INTESTINAL PROTOZOA OF MONKEYS AND MAN ROBERT HENNER and H J CHU, Am J Hyg 12 62, 1930

The objects of this investigation were to determine whether wild monkeys are parasitized with intestinal protozoa as captive monkeys are known to be, and to compare these protozoa with species that occur in man with special reference to specific identity. The digestive tract of forty-four wild Philippine monkeys of the species *Macacus philippinensis* (twenty-eight males and sixteen females) was examined immediately, or within three hours, after death, the vaginas of the females were also examined. The data recorded in this paper furnish evidence that is considered insufficient to separate as distinct species the eleven types of protozoa described from wild Philippine monkeys and the corresponding eleven types that live in man.

AUTHORS' SUMMARY

EPIZOOTIC FOX ENCEPHALITIS R G GREL, Am J Hyg 12 109, 1930

A summary is presented of the physical signs and symptoms, histologic observations, etiology, transmissibility and immunology of epizootic fox encephalitis in 125 foxes.

P H GUINAND

THE SUSCEPTIBILITY OF AFRICAN MONKEYS TO YELLOW FEVER JOHANNES H BAUER and ALEXANDER F MAHAFY, Am J Hyg 12 155, 1930

Attempts were made to infect African monkeys of four different species, *Cercopithecus tantalus*, *Cercopithecus mona*, *Cercocebus torquatus* and *Erythrocebus patas*, with yellow fever, both by the injection of virulent blood from infected rhesus monkeys and by the bite of infected *A. aegypti*. None of the animals succumbed to infection with yellow fever, but for a number of days the virus persisted in the blood of all except *Cercopithecus mona*, and it could be recovered again by the injection of their blood into susceptible rhesus monkeys. Two of the species, *Cercopithecus tantalus* and *Cercocebus torquatus*, were found definitely

capable of transmitting the infection to normal *A. aegypti*, the results with *Erythrocybus patas* in this respect were suggestive, but not definite, and no attempts were made to infect mosquitoes from *Cercopithecus mona*. Five monkeys, representing three different species, were bled before and after the experimental infection, the specimens of serum taken before the infection showed no protective properties, whereas those taken afterward protected rhesus monkeys, in 5 cc amounts, against a relatively large dose of the virus.

AUTHORS' SUMMARY

STUDIES ON THE FILTRABILITY OF YELLOW FEVER VIRUS JOHANNES H. BAUER and ALEXANDER F. MAHAFFY, Am J Hyg **12** 175, 1930

Yellow fever virus, both in the blood of infected monkeys and in infected mosquitoes, was found to pass through Berkefeld filters of all grades without a marked diminution in concentration, and also through Chamberland L-11 candles. No evidence was found to indicate that virus in blood differs from that in mosquitoes. The virus dies out rapidly when suspended in 0.9 per cent solution of sodium chloride, Locke's solution, Ringer's solution, hormone broth or distilled water, but it was found that when 10 per cent or more of normal rhesus serum is added to saline or distilled water, the deleterious effect of these mediums on the virus is much reduced.

AUTHORS' SUMMARY

A REPORT ON A CASE OF GIARDIASIS H. TSUCHIYA and JUSTIN ANDREWS, Am J Hyg **12** 297, 1930

The pathogenicity of *Giardia lamblia* is still open to question. The present report represents one instance in which the flagellate seems to have played a pathogenic role.

AUTHORS' SUMMARY

THE RÔLE OF THE LEUCOCYTES IN TUBERCULOSIS BENJAMIN L. BROCK, Am Rev Tuberc **21** 745, 1930

Periodic studies of the total and leukocytic counts often give a truer picture of the tuberculous condition than does the clinical course of the case. The neutrophil plays the part in the formation of tuberculous abscesses. Elevation in the percentage of neutrophils over a period of time is indicative of breaking down of tissue with the formation of abscesses. The total count, with the percentage of neutrophils, denotes the degree of activity. The lymphocyte plays the important role in the healing of the lesion. A definite increase in the percentage of lymphocytes, when the neutrophils remain around normal over a given period, is indicative of healing. In such cases the monocytes are found within normal limits. The monocyte plays the chief role in new tubercle formation. Elevation in the percentage of monocytes is rather consistent in cases showing a definite elevation in the percentage of neutrophils. Such a picture indicates spread of the disease with the formation of abscesses. Clinically active tuberculosis and progressive pathologic disease respond with septic types of leukocytic pictures. No definite role has as yet been ascribed to the eosinophil or the basophil.

H. J. CORPER

THE LEUCOCYTIC INTERPRETATION OF MEDLAR IN TUBERCULOSIS WILLIAM H. OATWAY, JR., Am Rev Tuberc **21** 786 1930

The scheme and limits of Medlar prove more sensitive than any other classification available when other causes of leukocytosis are absent in a tuberculous person. An excess of neutrophils, the septic picture, indicates the most severe and dangerous process. An increase in monocytes in an otherwise normal count, the hyperplastic type, is a more favorable passive type. The normal, inactive, leukocytic picture is evidence that the lesion is being well controlled. An increase of lymphocytes, giving the resistant picture, indicates a healing lesion. Eosinophils

and basophils had no demonstrable relation to the progress or severity of the cases. The types used in the interpretation by Medlar seem sufficient when intelligently used to show the action of the whole pathologic process. H. J. CORPER

THE EFFECT OF ULTRAVIOLET IRRADIATION ON TUBERCULOUS PERITONITIS IN GUINEA PIGS. M. MAXIM STEINBACH, ALFRED F. HESS and MILDRED WEINSTOCK, *Am Rev Tuberc* **22** 35, 1930

When guinea-pigs are infected with mildly virulent tubercle bacilli intraperitoneally, extensive tuberculous disease develops, even though they are subsequently treated with ultraviolet irradiation. In the animals that received irradiation, tuberculosis developed to the same degree as in those that had not been treated with the ultraviolet rays, and in some instances they showed more extensive disease than did the controls. H. J. CORPER

CHEMICAL CHANGES FROM GROWTH OF BOVINE TUBERCLE BACILLI ON LONGS MEDIUM. ALICE G. RENFREW, KATHLEEN M. HARRING and TREAT B. JOHNSON, *Am Rev Tuberc* **22** 116, 1930

The growth of bovine tubercle bacilli was followed for sixteen weeks. Carbohydrate combinations, as judged by the copper-reducing properties of the cultures, made their appearance after the third week of growth. The analytic values for reducing sugars after hydrolysis were much higher for bovine bacilli than for avian and timothy cultures, but less than half the value determined for the human strain, H37. H. J. CORPER

THE GROWTH-PROMOTING PRINCIPLES IN THE POTATO. NAO UYLI, *Am Rev Tuberc* **22** 203, 1930

Practically all of the active principles in potato for the growth of tubercle bacilli in vitro are to be found in the residue of the potato after its extraction with the common organic solvents, such as acetone, alcohol or ether. Investigation of the effects of the various elements known to be present in the potato revealed two classes of stimulants for the growth of tubercle bacilli. One class is represented by inositol, maltose and dextrose, and is termed metabolic stimulants, because the substances stimulate the growth of tubercle bacilli only when the bacilli are present in large numbers, while the other class of stimulant is represented by soluble starch and dextrin, and is termed reproductive stimulants, because the substances not only stimulate the growth of tubercle bacilli when these are present in large numbers, but also in small numbers. Glueogen does not appear to possess the property of stimulating the growth of tubercle bacilli in vitro, and future studies will be required further to elucidate this. H. J. CORPER

STREPTOTRICHOSIS. I. J. SINGER and HARRY C. BAILEY, *Am Rev Tuberc* **22** 233, 1930

A case of streptotrichosis, possibly primary in the lungs, is reported. *Streptothrix* was found in the gums, sputum pus from superficial abscesses and, at autopsy, in practically every organ of the body. Throughout the illness there was a persistent and unexplained purpura. The lesion in the lung was associated with pulmonary tuberculosis. Tubercle bacilli were demonstrated from direct smear in pus obtained from the abscess cavities, but at no time during the course of the disease could they be demonstrated in the sputum. The lesions in the lung showed the characteristic nodular formation with necrosis and the formation of abscesses. There were few proliferative changes and consequently little or no evidence of bronchiectasis. The character of *Streptothrix* in this case is reported separately. H. J. CORPER

PRIMARY ASPERGILLIOSIS OF THE LUNGS LEO V SCHNEIDER, *Am Rev Tuberc* **22** 267, 1930

Aspergillus fumigatus produces pulmonary lesions resembling those of fibroid tuberculosis. Differential diagnosis is particularly difficult when aspergillus infection is secondary to any respiratory infection. Aspergillus infection is transmitted from pigeons and parrots, and is also observed in hair-combers who use rye flour to remove grease from the hair. Animals inoculated with spores from a pure culture of *Aspergillus fumigatus* showed typical lesions at autopsy. Tuberculin tests are of no diagnostic value because aspergillosis gives the same local reaction as tuberculosis. Iodides seem to be specifically destructive to the life and growth of the aspergillus fungus.

H J CORPER

STUDIES IN BACTERIAL METABOLISM A I KENDALL, T E FRIEDEMANN and M ISHIKAWA, *J Infect, Dis* **47** 186, 1930

"Resting" bacteria are defined as organisms that are fully mature and endowed with their full potentiality for metabolism, but constrained from multiplication by the withholding of substrates essential for their continued growth. It is inferred, therefore, that "resting" bacteria initiate changes in substrates that they, as proliferating bacteria, will subsequently use for their energy requirements. The details for cultivating, harvesting and testing the chemical activity of suspensions of "resting" bacteria are discussed in detail. Quantitative studies of the action of suspensions of certain representative bacteria were made, dextrose, lactic acid, pyruvic acid and alanine being used as substrates, singly and in combination, in the presence and absence of oxygen, and in the presence and absence of methylene blue (methylthionine chloride, U S P). The determinations comprised the quantitative partition of these substances under the various conditions enumerated, together with the quantitative determinations of volatile acids and carbon dioxide. The outstanding facts were as follows:

Bacteria that ferment dextrose habitually, as *Bacillus coli*, *B. pyogenes-foetidus* and *Staphylococcus aureus*, as "resting" bacteria, transformed dextrose rather vigorously. There was a concomitant but not an equimolecular increase in lactic acid.

Bacteria that do not utilize dextrose as *B. alcaligenes* and *Vibrio* H/61, did not, as "resting" bacteria, induce a measurable change in the dextrose molecule.

B. pyocyaneus, which ferments dextrose less readily than most bacteria in the "resting" state, decomposed this substance readily in the presence of oxygen. In the absence of oxygen, practically no dextrose was transformed.

Pyruvic acid was energetically decomposed by the bacteria that fermented dextrose. *B. pyocyaneus*, which is not an active fermenter of dextrose, transformed pyruvic acid rather vigorously. In the absence of oxygen, "resting" *B. pyocyaneus* decomposed pyruvic acid, even though dextrose was not attacked under anaerobic conditions. It is surmised, therefore, that pyruvic acid is formed when "resting" bacteria are acting on dextrose but fails to accumulate because it is utilized nearly as rapidly, during the process of fermentation of dextrose.

Nonfermenting bacteria, exemplified by "resting" *B. alcaligenes* and *Vibrio* H/61, failed to produce a discernible change in pyruvic acid.

Lactic acid was decomposed by all the bacteria studied. Generally speaking, the loss in lactic acid was greater in the presence than in the absence of oxygen. It appears to be significant that "resting" *B. alcaligenes* and *Vibrio* H/61 transformed lactic acid nearly quantitatively to pyruvic acid. These bacteria did not ferment dextrose. On the other hand, the fermenting bacteria, previously enumerated, although transformers of lactic acid, failed to record a proportionate increase in pyruvic acid. As pyruvic acid disappeared rapidly in the presence of "resting" bacteria of the fermenting type, it is possible that it was formed and transformed at nearly equal rates.

Alanine was not a particularly favorable substrate for the fermenting bacteria. However, *B. alcaligenes* appeared to transform it fairly readily.

It is suggestive, if not significant, that both gas-producing and nongas-producing fermenting bacteria exhibit qualitative similarity in their respective activities as "resting" bacteria on the substrates examined, especially dextrose and pyruvic acid. The aerogenic organisms, exemplified by "resting" *B. coli*, appear to initiate the attack on the dextrose molecule in the same manner as the nonaerogenic fermenting bacteria, exemplified by "resting" *B. pyogenes-foetidus* and *Staphylococcus aureus*. Therefore, the exuberant production of gas (hydrogen and carbon dioxide) would seem to be a terminal reaction, not manifested by "resting" bacteria.

In the presence of oxygen, methylene blue appears to increase somewhat the action of "resting" bacteria, both of the fermenting and of the nonfermenting type, on lactic acid. In the absence of oxygen, the transformation of lactic acid is materially increased, even the nonfermenting type, as *B. alcaligenes*, decomposes considerable lactic acid in the presence of methylene blue, but in the absence of oxygen. As pyruvic acid is formed in the latter instance, it is assumed that suspensions of "resting" *B. alcaligenes* dehydrogenate lactic acid to pyruvic acid, thereby becoming hydrogenated. Methylene blue dehydrogenates the "resting" bacteria in turn, becoming reduced thereby to leukomethylene blue. There is evidence that methylene blue exerts some harmful influence on "resting" bacteria.

"Resting" bacteria of the dextrose-fermenting type, exemplified by suspensions of *B. coli*, *B. pyogenes-foetidus* and *Staphylococcus aureus*, appear to transform at least some pyruvic acid to lactic acid. Nonfermenting types, for example, "resting" *B. alcaligenes* and *Vibrio* H/61, have little action on pyruvic acid, in fact, the reaction proceeds nearly quantitatively in the opposite direction, lactic acid to pyruvic acid. As the transformation of pyruvic acid is reminiscent of the action of the tissue enzyme, glyoxalase, which transforms methylglyoxal, an aldehyde corresponding to pyruvic acid, to lactic acid, it was surmised that the two processes might be somewhat analogous. Experiments made with "resting" bacteria indicate that those organisms in the "resting" state which do ferment dextrose have a distinct glyoxalase-like action. Those which fail to transform dextrose, and which also fail to act on pyruvic acid, are devoid of glyoxalase-like action. It was also shown that suspensions of "resting" bacteria cultivated for considerable periods of time in the presence of dextrose have, as "resting" bacteria, distinctly more intense glyoxalase-like activity than suspensions of corresponding strains developed in the absence of dextrose. The magnitude of chemical change induced by the fermenting strains, which stands in distinct contrast to the inactivity of the nonfermenting strains measured under parallel conditions, would appear to justify the general conclusion that the former (dextrose-fermenting) organisms in the "resting" state exhibit definite glyoxalase activity, whereas the latter (nondextrose-fermenting) organisms in the "resting" state are devoid of glyoxalase activity.

AUTHORS' SUMMARY

THE UTILIZATION OF CERTAIN SUBSTITUTED CARBOHYDRATES BY BACTERIA A. I. KENDALL and C. E. GROSS, J. Infect. Dis. 47:249, 1930

This investigation is a qualitative study of the effect of definite alteration in certain carbohydrate molecules on their utilization by specific bacteria. The series of compounds considered included derivatives of d-dextrose, d-mannose and fructose of the hexose series, d-galactose, d-arabinose and l-arabinose, d-xylose and glycerin. The most significant fact deduced was that any departure from the configuration of the d-dextrose molecule decreases its utilizability by common bacteria. Oxidation of d-dextrose to gluconic acid or to glucuronic acid is less potent in reducing utilizability than reduction of the d-dextrose molecule to sorbitol. Substitution of from one to four methyl groups in the molecule makes the resulting compound refractory to microbic attack. The same generalization holds for mannose and galactose, except that mannitol, the alcohol of d-mannose, is distinctly more utilizable than sorbitol, the alcohol derivative of d-dextrose. Galactose is fermented by a greater variety of bacteria than either mannose or fructose. In this respect it appears to stand next to dextrose. This is significant in light of

the fact that galactose does not have a common enol with dextrose, formerly it was held that hexoses having a common enol are mutually fermentable. In this connection, the nonfermentability of gamma trimethyl xylose, chemically a very reactive sugar, is of interest as suggesting that even intense chemical reactivity is not of itself a criterion on which to predicate biologic utilizability. An unexpected instance of protoplasmic versatility seems to be shown in the mutual fermentation of d-arabinose and its precise opposite, l-arabinose. In light of current views of protoplasmic orientation and polarity, this observation is unexplainable, and should be repeated.

AUTHORS' SUMMARY

THE PRODUCTION OF HISTAMINE BY CERTAIN STRAINS OF THE GAS BACILLUS
A. I. KENDALL and E. GEBAUER, *J. Infect. Dis.* **47** 261, 1930

Histamine was isolated as the picrate from milk cultures of a strain of the gas bacillus. The analysis of the picrate for carbon, hydrogen and nitrogen was in reasonable accord with theoretical values. Further identification of this picrate was had from the Pauly reaction, and the physiologic action on smooth muscle, both qualitatively and quantitatively. Only certain strains of the organism produce histamine.

AUTHORS' SUMMARY

A STUDY OF BACTERIUM DYSENTERIAE, SONNE TYPE S. A. KOSER, D. O. REITER, E. BORNIKER and E. I. SWINGLE, *J. Prev. Med.* **4** 477, 1930

The Sonne dysentery bacilli appear to constitute a distinct type on the basis of both physiologic characteristics and agglutinative relationships. The nineteen Sonne cultures included in the present study possessed the property of fermenting the following sugars with production of acid: dextrose, lactose (slow), sucrose (slow), usually raffinose (slow), arabinose, rhamnose, levulose, mannose, galactose, maltose, trehalose, mannitol and glycerol. Negative results occurred with xylose, melezitose, dulcitol, sorbitol, adonitol, erythritol, salicin and inulin. It is probable that dextrin is only sparingly utilized, if at all. All the Sonne cultures gave negative results in tests for the formation of indol, showed no liquefaction of gelatin or digestion of starch and gave no evidence of the production of hydrogen sulphide in a dextrose agar sulphite ferric chloride medium. Nitrates were reduced to nitrites. A number of other dysentery-like organisms described under a variety of names were found to be identical with the Sonne type in every respect. One of the most striking characteristics of the Sonne cultures was the slow production of acid from lactose and sucrose—a property shared by certain other, miscellaneous cultures, including the dispar type. The two dispar cultures studied in this investigation differed from the Sonne strains in their ability to attack xylose and sorbitol and to form indol. They were also distinct serologically. Both types may be readily distinguished from the Flexner organisms. A review of the recorded isolations of the Sonne type shows that it has been found in many localities in association with dysentery or dysentery-like conditions, particularly those of infants.

AUTHORS' SUMMARY

BACTERIAEMIA FOLLOWING OPERATIONS ON THE URETHRA. F. J. F. BARRINGTON and HEDLEY D. WRIGHT, *J. Path. & Bact.* **33** 871, 1930

Invasion of the blood stream by bacteria is a common occurrence following operations on the urethra, and this can be recognized within a few minutes after the operation. The organisms come from the urinary passages, and the invasion is conditioned in part by the numbers of organisms in the urine and in part by the facilities afforded for invasion by tissue damage. Similar invasion may occur later after natural micturition and may be of much higher grade. Fever and rigors do not necessarily follow such blood invasions but appear to depend on the size of the blood invasion. When a rigor occurs it is at an interval after the blood invasion, and at the time of the rigor the blood may be sterile.

AUTHORS' SUMMARY

INFLUENCE OF CALCIUM ON MICROBIC SPECIES PAUL BORDET, Ann de l'Inst Pasteur **45** 26, 1930

Deprivation of calcium profoundly modifies certain microbic species, e g, it exaggerates sporulation regularly and in marked degree. A microbic species composed of two races, unequally sporogenous, shows, under the influence of oxalate medium, a predominance of the sporogenous variety. Calcium appears, then, to be one of the factors in microbic variation. It is, seemingly, a disturbance of this variability which explains the distinct increase in the chromogenesis of *Chromobacterium prodigiosum* under the influence of a lack of calcium. This determines, with certain bacilli, considerable morphologic variation, transforming them into short rods and often into coccobacilli. The modifications determined by the use of oxalate medium have as a distinctive feature the failure to produce any alteration in hereditary potentialities, replaced in contact with calcium, the organism immediately resumes its normal characteristics. This contribution furnishes nineteen figures in color.

AUTHOR'S SUMMARY

A BACILLUS OF CUTANEOUS GANGRENE R NATIVELL, Ann de l'Inst Pasteur **45** 169, 1930

Mihan's *Bacillus gangraenae-cutis* was isolated in fourteen cases of true cutaneous gangrene. The organism, which is completely described, is a gram-negative rod, with a tendency to bipolar staining, it shows motile, peritrichous flagella, it is nonsporulating and in older cultures it occurs as long filaments. It grows easily on the usual mediums, the optimum temperature being about 37 C. The organism is aerobic, it is also a facultative anaerobe. It produces a fetid odor. It survives some months in cultures. Biochemically, the results recorded are very irregular. In general, the organisms isolated were proteolytic, nonhemolytic in mediums and rather weakly saccharolytic. A definite toxin was not demonstrated. Agglutination and complement-fixation showed great variation and no group specificity, and no relationship to *Pseudomonas pyocyanea*, *Bacterium coli* or *Proteus vulgaris*, to which the organism might be related. Treatment with specific serum, as well as with specific intravenous injections of arsphenamine, is suggested (illustrated in an experimental lesion in a rabbit).

The pathogenicity is variable in degree. Though the organism is common and responsible for some histologic changes, the role is apparently that of a secondary invader. Post mortem, the gangrenous and ulcerative condition seems confined to the superficial layers, being never observed deep in the muscle. Histologically, a sharply delineated massive infiltration occurs, with the arterioles unaffected. A black pigment is deposited in the liver and the spleen. The lesions are duplicated in lesions induced experimentally in guinea-pigs or in rabbits. Subcutaneous injection of the organisms into guinea-pigs is followed by edematous swelling and purpuric spots. In forty-eight hours a blackish, well defined lesion appears, 5 or 6 cm in diameter, which passes through various ulcerative stages to complete cure in from fifteen days to three weeks. The reaction is local (illustrated by plates). Similar lesions may be produced in rabbits, which respond, perhaps, more vigorously.

M S MARSHALL

ONE OR SEVERAL RABIES VIRUSES P REMINGER and J BAILLY, Ann de l'Inst Pasteur **45** 376, 1930

By analogy, there might be several types of rabies virus, as there are in the case of numerous bacterial agents of infection, or variations in these agents. Following suggestions made at the international conference on rabies (1927) cases have been noted in which apparent failure of cross-protection indicates discrepancies suggesting the existence of several strains of virus. A study of strains of virus from various locales in rabbits leads the authors to uphold the stability of a single virus, remarking, "If one uses in intensification and preservation (of the virus) a fraction

of the time which certain authors advocate spending in the preparation of polyvalent vaccines or autogenous vaccines, one will have no cause to regret it.' A virus derived from an original Pasteur strain, now in its 2480th passage, regularly used by the authors at their Pasteur Institute in Tangiers, is cited

M S MARSHALL

THE CORRELATION BETWEEN TUBERCULOUS DISEASE AND THE GENERATIVE PROCESSES IN THE FEMALE ORGANISM JOACHIM GRANZOW (Berlin S Karger, 1930)

This monograph with bibliography is a supplement to the *Monatschrift für Geburtshilfe und Gynäkologie*. The thesis is based on a comprehensive study of nonpregnant, pregnant and puerperal guinea-pigs infected with attenuated tubercle bacilli by way of the right ventricle. The conclusions are as follows: 1 The normal quiescent uterus has a marked resistance against hematogenous infection with tubercle bacilli, while in pregnancy and puerperium the uterus is more frequently involved. 2 Hematogenous infection, in the majority of cases, leads to abortion, premature labor or stillbirth.

Granzow considers the abortions to have been an expression of resistance to infection, but bacilli might readily have entered the intervillous spaces of the placenta. Nonspecific and severe degenerative changes of the ovarian parenchyma were frequently present, and interfered with ovulation. The ovarian changes ran parallel with the severity of the disease. The lymph glands were not as often tuberculous during pregnancy as in puerperium. The liver, spleen, kidneys, heart and mammary glands were more frequently involved in pregnant—especially during the puerperium—than in nonpregnant animals. On the other hand, the lungs of the guinea-pig were more resistant to tuberculosis during the pregnant state. The functional changes of pregnancy in certain organs increased their disposition to tuberculosis, and this was true especially of the mammary glands. In resistance to tuberculosis, the endocrine glands were not, as a rule, severely affected by pregnancy.

A J KOBAR

CULTURE OF THE TUBERCLE BACILLUS M MALKANI, Beitr z Klin d Tuberk 73 395, 1930

Known amounts of tubercle bacilli were seeded on egg mediums according to Lubenau-Hohn, Petroff and Petragham's medium. It was found that Lubenau-Hohn's medium and that of Petroff yielded equally good results, while Petragham's medium was disappointing. The number of colonies in the latter always remained far below the number of seeded organisms.

MAX PINNER

A CASE OF PULMONARY ASPERGILLOSIS R BERGMAN and F HENSCHL, Beitr z Klin d Tuberk 73 467, 1930

A woman had the symptoms of a chronic pulmonary disease for twenty years. For the last ten years, in various hospitals, her condition had been diagnosed as far advanced pulmonary tuberculosis. The clinical course was very chronic, in spite of the extensive lesion, and the general condition of the patient remained fair, in spite of a major operation and a chronic renal disease. She had frequent hemoptysis. Tubercle bacilli were never demonstrable in the sputum. At necropsy a pulmonary infection with *Aspergillus fumigatus* was found. The molds were found chiefly in preformed cavities, and they did not show any tendency to infiltrative growth. The hemoptyses were probably caused by richly vascularized granulation tissue in the walls of cavities. A source of infection of the usual type was not demonstrable.

MAX PINNER

CONGENITAL TUBERCULOSIS M ZARIL, Beitr / Klin d Tuberk **74** 380, 1930

A case of congenital tuberculosis is reported Sixteen days after birth the tuberculin reaction was positive Clinically the disease began with abdominal symptoms The infant died when it was 39 days old At necropsy a primary complex was found in the liver, with extensive caseation of the portal lymph nodes The primary focus showed deposits of lime and fibrous encapsulation The milary tubercles in the lung were all of the exudative type

MAX PINNER

Immunology

THE SENSITIZATION OF CATTLE TO TUBERCULIN BY OTHER THAN TUBERCLE BACILLI E G HASTINGS, B A BEACH and ISABEL THOMPSON, Am Rev Tuberc **22** 218, 1930

A number of cultures have been isolated from the tissues, usually lymph nodes, of cattle which have reacted to tuberculin, but which have shown no evidences of the disease on postmortem examination When injected into tuberculosis-free cattle, these cultures cause sensitization to tuberculin, which condition is, in most cases, evanescent The cultures were proved free from tubercle bacilli before use in cattle through the injections of guinea-pigs, rabbits and fowl The cultures produce no lesions in cattle The observations indicate that a positive response to tuberculin in cattle is not absolute proof of infection with tubercle bacilli Some other of the mycobacteria may invade the tissues and cause sensitization to tuberculin

H J CORPES

LOCAL IMMUNITY OF THE PERITONEUM IRVING A FRISCH, Arch Int Med **46** 410, 1930

A modification of the phenomenon of local skin reactivity introduced by Schwartzman is described in this report This modification consists in the employment of an intraperitoneal instead of an intravenous injection of toxic substance twenty hours after such a preliminary inoculation into the skin By means of this modification, the principle of local peritoneal immunity was demonstrated Rabbits in which the intraperitoneal injection of *B typhosus* culture filtrate was able to elicit the Schwartzman phenomenon in previously prepared skin sites were rendered negative to this phenomenon by repeated injections of this culture filtrate intraperitoneally It was then shown that this reaction of the skin could still be produced if the reacting factors were introduced intravenously It must thus be concluded that the immunity produced under these circumstances was of a distinctly local character involving only the peritoneum, and that the entire organism was not yet immune It was also determined that between three and four injections of *B typhosus* culture filtrate were necessary to render the peritoneum immune to this filtrate

AUTHOR'S SUMMARY

TRANSFUSION FROM A GROUP A DONOR TO A GROUP B RECIPIENT WITHOUT FATAL RESULT LYMAN BURNHAM, Arch Int Med **46** 502, 1930

A full transfusion (400 cc into a recipient weighing but 85 pounds) of group A blood into a group B recipient was accidentally performed, with only slight symptoms coughing, oppression in the chest, slight dizziness and pain in the lumbar regions The incompatible transfused blood remained in the circulation of the recipient for from three to five days The absence of serious consequences was shown to be due to the fact that all of the group-specific iso-agglutinin α in the recipient's serum was entirely incapable of clumping the group A cells of the donor at body temperature, although it clumped these cells vigorously at room temperature

AUTHOR'S SUMMARY

CHARACTERISTICS OF NATURAL AGGLUTININS H J GIBSON, J Hyg **30** 337, 1930

A study has been made of natural agglutination as exemplified by the reactions of the serum of nine animal species with a variety of bacteria

AUTHOR'S SUMMARY

HETEROPHILIC ANTIBODY IN HUMAN SERUM AND THE SKIN REACTION TO GUINEA-PIG SERUM SUSAN GRIFFITH RAMSDELL, J Immunol **19** 341, 1930

Guinea-pig serum, used as a native heterophilic antigen, occasioned reactions of the skin of the immediate type, with regularity, in a group of patients with disturbances of the skin believed to be allergic. In the normal group, this reaction appeared in about half the members. The presence of agglutinin for sheep cells was a regular finding in the allergic group in titers considerably higher than that found in the normal. The hemolysin titers did not vary with the groups. No correlation could be established between the occurrence of a reaction of the skin to guinea-pig serum and the heterophilic antibody titers. Suspensions of haptene and lecithin did not occasion a marked reaction in any instance. The submaximal response could not be correlated with any other observation. The response of the skin to guinea-pig serum could not be identified as a reaction between human heterophilic antibody and a native heterophilic antigen assumed to be contained in the guinea-pig serum.

AUTHOR'S SUMMARY

MOLECULAR MOVEMENT, VISCOSITY AND AGGLUTINATION STEPHEN WENT, J Immunol **19** 347, 1930

The viscosity of the dispersing medium affects the Brownian movement of bacteria a great deal. Above a certain degree of internal friction, molecular movement ceases. The intensity of this movement depends also on the absolute temperature. Bacteria may flocculate spontaneously if the viscosity of the medium is increased to a certain degree. In this relation different micro-organisms show different sensitiveness, which seems to depend on the dimension of the bacterial surface. Mediums of higher viscosity hinder the bacterial agglutination caused by immune serum, this is an effect on the first phase of the immune agglutination, i. e., on the process of adsorption of the immune bodies.

AUTHOR'S SUMMARY

IMMUNOLOGIC STUDIES IN BLASTOMYCOSIS ANNA DEAN DULANEY, J Immunol **19** 357, 1930

In the usual course of infection with *Blastomyces dermatitidis* antibodies do not seem to be formed to any appreciable degree. The production of antibodies may be stimulated by the use of an autogenous vaccine. In the case of one patient, marked improvement followed the use of the vaccine. The highest titer of complement-fixing antibodies was demonstrated at the time when the patient showed the most marked clinical improvement. With progress of the disease, the antibody titer decreased. Antibodies, chiefly complement-fixing substances, may be experimentally produced in rabbits on injection of the *Blastomyces* antigens. The mycelial, oidial and yeast forms of the same strain of *Blastomyces* stimulate identical antibodies. No species-specificity could be demonstrated in *Blastomyces*. Slightly positive results were obtained with closely related yeasts. Specific results were obtained on titration of the serums.

AUTHOR'S SUMMARY

ANTIGENIC ANALYSIS OF CULTURES OF *B. PARADYSENTERIAE* AND *B. MORGANI* G. M. MACKENZIE and LOUISE N. BATT, J. Immunol. **19** 371, 1930

B. paradyenteriae and *B. morganii* were found in an outbreak of summer diarrhea. Normal agglutinins for the dysentery group were found in horse, rabbit and human serums. They were only present in horse serum for *B. morganii*. A study of agglutinins in the serums of patients failed to give evidence that these two organisms were the cause of the infection. Cross-agglutination and absorption tests with immune serums showed the five strains of *B. paradyenteriae* to be the same. In this manner four cultures of *B. morganii* were shown to represent three different strains. The *B. paradyenteriae* isolated during the epidemic contained an antigenic component which was present in one culture of *B. morganii*.

EDNA DELVES

BACTERIAL PRECIPITIN REACTION AND THE RAMON FLOCCULATION ELIZABETH LEE HAZEN, J. Immunol. **19** 393, 1930

Flocculation in mixtures of filtrate of *C. diphtheriae* and antitoxin is not limited by agglutination types (211) of the organisms which serve for the production of toxin. Precipitation in mixtures of toxic filtrate and agglutinating serum is restricted to agglutination types. Removal of the nontoxic precipitinogens from the toxic filtrate after contact with a specific precipitating serum has little, if any, effect on the Lf of the toxin, but prevents subsequent precipitation of the filtrate with the homologous precipitating serum. The property in the toxic filtrate essential for flocculation with antitoxin is destroyed at a temperature of 60 C for one-half hour, whereas the property essential for precipitation of agglutinating serum is not destroyed at a temperature of 85 C for one hour. Removal of the bacterial antibody from antitoxic serum by adsorption of the serum with bacterial extracts does not prevent subsequent flocculation of the serum with the toxic filtrate, whereas the agglutinating serum treated in the same manner no longer precipitates with the toxic filtrate. The Ramon reaction is probably due to interaction between toxin and antitoxin and not between bacterial precipitinogen and precipitin.

AUTHOR'S SUMMARY

ON THE DIALYZABILITY OF PROTEINS ARTHUR F. COCA, J. Immunol. **19** 405, 1930

The dialyzability of the excitants of atopic hypersensitiveness in egg white reported by W. Jadassohn is confirmed. With the aid of specific antisera and chemical methods the dialyzable excitants are shown to be native proteins. The proteins in the dialysate are antigens.

AUTHOR'S SUMMARY

THE TRANSFER OF THE SKIN-REACTING ANTIBODY IN HUMAN SERUM TO GUINEA PIG SKIN SUSAN GRIFFITH RAMSDELL, J. Immunol. **19** 411, 1930

A specific reaction in the skin of the guinea-pig may be obtained, with fair regularity, when the test antigen can be used in a considerable concentration, on transfer of the serum of asthmatic subjects to the skin of the animal. The serums of patients with hay-fever, urticaria and eczema only occasionally transfer this reaction. This failure is ascribed to a relatively low antibody content in such serums and to the limitations of the technique used.

AUTHOR'S SUMMARY

THE EFFECT OF NORMAL SERUM ON ANTIPNEUMOCOCCUS SERUM, TYPE 1 O. H. ROBERTSON, RICHARD H. P. SIA and M. AGNES CORNWELL, J. Immunol. **19** 429, 1930

With a view to obtaining a clearer understanding of the environmental conditions under which pneumococcus immune serum exerts its optimum antibacterial action a study was made of the influence of fresh normal serum on the

pneumococcal-promoting action of antipneumococcus serum type 1 in normal rabbit serum-leukocyte mixtures. It was found that the substitution of inactivated normal adult rabbit serum for fresh serum largely deprived the immune serum of its power to confer pneumococcus-destroying properties on the serum-leukocyte mixtures. In the absence of fresh serum, relatively high concentrations of immune serum had to be employed to produce a demonstrable killing effect. However, if instead of adult rabbit serum inactivated serum of young rabbits was used, the pneumococcal-promoting action of the immune serum was completely abolished. This could be restored by the addition of relatively small quantities of fresh serum to the inactivated serum-leukocyte mixture. Furthermore, there was found to be a constant quantitative relationship between the effective dilution of immune serum and the amount of fresh serum necessary, the higher the dilution of immune serum the greater was the quantity of fresh serum required to make it effective. It was shown that the interaction of pneumococcus antigen and antibody in the normal serum deprived it of activating properties. Observations were then made to determine whether or not a similar diminution occurs in the body during the course of pneumococcus infection. Tests on the serum of experimentally infected animals and from cases of lobar pneumonia in man showed no notable impairment of its activating function.

AUTHORS' SUMMARY

THE COMPARATIVE VALUE OF ROUGH AND SMOOTH STRAINS OF *B. TYPHOSUS* IN TYPHOID VACCINES. FRANCIS B. GRINNELL, *J. Immunol.* **19** 457, 1930

The customary course of prophylaxis with a vaccine made from a rough strain of *B. typhosus* "Rawlins" produces little or no increase in the bactericidal power of the blood. A similar course of treatment with a vaccine made from a smooth, virulent strain of *B. typhosus* causes a considerable increase in the bactericidal antibodies. So far as the bactericidal test is an index of the resistance of the patient, typhoid vaccine in which rough strains of the organism are employed are valueless for prophylaxis. Vaccination with rough strains leads to the production of agglutinins for the virulent strains with no increase in the bactericidal power of the blood. Agglutination is therefore not an adequate test of the resistance of the person.

AUTHOR'S SUMMARY

ON THE HEAT STABILITY OF THE DIPHTHERIA TOXIN. K. ANDO and H. NISHIMURA, *J. Immunol.* **19** 465, 1930

The heat sensitiveness of the diphtheria toxin depends on its own pH under which it is heated. The more acidified the toxin, the more heat-stable it is. Diphtheria toxin is practically destroyed by heating it to 80 or 90 C for thirty minutes, but not completely even by boiling for thirty minutes. When it was acidified to a pH of 2 prior to boiling, about $\frac{1}{1000}$ to $\frac{1}{700}$ of its original toxicity remained after boiling for thirty minutes. Accordingly, the property of heat sensitiveness accepted hitherto as such must not be considered as a general characteristic of bacterial exotoxins.

AUTHORS' SUMMARY

CONCENTRATION OF ANTIPNEUMOCOCCIC AND ANTIMENINGOCOCCIC SERUMS. KENNETH GOODNER, *J. Immunol.* **19** 473, 1930

In the course of immunization of horses against the meningococcus and the pneumococcus there is generally an increase in the serum of euglobulin of low solubility. The antibody of the immune serum is associated with this protein. Certain of the solubility characters of this antibody euglobulin are reported, and it is shown that in most instances it is unnecessary to concentrate this protein as a whole, for the greater part of the antibody is associated with the least soluble fraction of this protein. A method, based on these studies, is given for the routine concentration of antipneumococcic and antimeningococcic horse serums.

AUTHOR'S SUMMARY

THE QUANTITATIVE RESPONSE OF INTESTINE FROM SENSITIZED GUINEA-PIGS TO HOMOLOGOUS PROTEIN AND TO HISTAMINE A I KENDALL and F O SHUMATE, J Infect Dis 47 267, 1930

A quantitative estimation of the degree of sensitization induced in guinea-pigs was reached by a determination of the minimal amount of homologous protein required to induce a maximal contracture in a series of strips of intestine taken from the sensitized animal. In making these tests, it is essential to use the ileal section of the gut, the duodenal end is distinctly less reactive both to contact with the homologous protein and to histamine

AUTHORS' SUMMARY

THE ANAPHYLACTIC REACTION IN SMOOTH MUSCLE A I KENDALL, J Infect Dis 47 284, 1930

A strip of isolated, surviving intestine from a highly sensitized guinea-pig may be thrown into a series of maximal contractures by alternately exposing the strips to diluted antigen and to fresh Tyrode solution. The contraction induced by the former is "washed out" in the latter. A time comes when the strip will no longer respond to even high concentrations of the antigen. This is construed as evidence of a desensitization. It will, however, still contract in characteristic manner in contact with a threshold stimulating dose of histamine. Desensitization, therefore, is regarded as a gradual exhaustion of a specific, "sessile" antibody resident in the smooth muscle of the intestine of the guinea-pig. The fact that after exhaustion of this hypothetical specific antibody, the smooth muscle will still shorten in response to a smooth muscle contractant, is regarded both as evidence of the quantitative character of the reaction and as an indication that the antibody is actually within the smooth muscle tissue, from which it cannot be removed readily by washing with physiologic solutions, but in which it may be exhausted by contact with the specific antigen. The bearing of these observations on the "histamine" theory of anaphylaxis is discussed.

AUTHOR'S SUMMARY

EXPERIMENTS WITH CERTAIN REACTIVE FACTORS OF ASCARIS HAMILTON R FISHBACK, J Infect Dis 47 345, 1930

Extracts of *Ascaris* in different solvents were found to possess a strong but variable hemolytic action on human red blood cells suspended in saline solution. Small doses of serum from young rabbits immunized against *Ascaris* substance completely inhibited hemolysis by the *Ascaris* extracts. Uterine strips from sensitized guinea-pigs responded specifically to the *Ascaris* extracts. After incubation with immune serum, the acetone-insoluble, alcohol-soluble extracts caused no excitation of the uterine strip, while the saline solution extract was still active. The exciting factor remaining in the latter extract was its protein content. In an allergic human subject, the results of intradermal tests with *Ascaris* extracts were positive. Here, also, the reactivity of the acetone-insoluble, alcohol-soluble extract was neutralized by immune serum, while that of the saline solution extract was not diminished. The immune content of the serum thus was specific against the toxin-producing hemolysis of red blood cells and against the oxytocic and skin reactive factors of the acetone-insoluble, alcohol-soluble *Ascaris* extract, but was ineffective against the saline solution extract.

AUTHOR'S SUMMARY

THE NEUTRALIZATION OF THE VIRUS OF POLIOMYELITIS BY HUMAN SERUM H J SHAUGHNESSY, P H HARMON and F B GORDON, J Prev Med 4 463, 1930

Human serums mixed, in various dilutions, with the virus of poliomyelitis were inoculated intracerebrally into monkeys of the genus *Macacus rhesus*. Serums from ten normal adults and six normal city children neutralized the virus in final

dilutions as high as 1:30, in a large majority of the tests. Serums from three of four rural children and four of five normal infants showed practically no neutralizing power. Serums from fourteen convalescents from poliomyelitis, even those recovered within two years, showed less neutralizing power than the serums of normal adults and normal city children. Serums from seven familial contacts of patients with poliomyelitis showed about the same neutralizing power as serums from normal adults. It is possible that immunity against poliomyelitis develops in a way similar to immunity against diphtheria. Tested normal serums may prove as effective as convalescent serum in the treatment of poliomyelitis.

AUTHORS' SUMMARY

ISOHAEMAGGLUTININS IN PREGNANCY KATHLEEN EDGEcombe, J. Path & Bact
33 963, 1930

The bloods of eighteen women have been tested at various periods of pregnancy from fifteen to forty weeks, and the bloods from their babies examined at birth. The fetus had a definite influence on the titer of the mother's blood as follows. With a fetus of no group at birth, the mother's blood showed little or no change during pregnancy, with a fetus of the same group, the mother's blood showed an increase of titer (cells + 16 per cent, serum + 86 per cent), with a fetus of a different group, the mother's blood showed a much greater rise in titer (cells + 83 per cent, serum + 330 per cent). Three bloods were tested from five to nine months after pregnancy. One that had shown no increase during pregnancy showed little alteration, and two in which there had been an increase during pregnancy showed a fall practically to the original level.

AUTHOR'S SUMMARY

ANAPHYLACTIC RESPONSES OF THE GUINEA-PIG'S SKIN C. E. KELLETT, J.
Path & Bact **33** 981, 1930

The response of the guinea-pig's skin to simple forms of trauma, to histamine and to trauma occasioned by local antibody-antigen reaction differs from that of man in that the arteriolar flare is rudimentary and barely detectable. The local response of the guinea-pig's skin to local reaction of antigen and antibody has been described under three main types which grade one into the other, and which seem to be, in the main, dependent on the local concentration of antibody. A generalized response of the skin occurs if the antigen is suitably introduced into a passively or actively sensitized guinea-pig. A similar response on or about the sixth day may follow on a single massive dose of antigen. After a dose of horse serum, guinea-pigs will die of acute anaphylactic shock on the introduction of anti-horse rabbit serum if an incubation period of at least three fourths of an hour is allowed.

AUTHOR'S SUMMARY

INTRADERMAL TESTS WITH EXTRACT OF LEPROUS SKIN S. LYLE CUMMINS
and J. J. DU PRL LE ROUX, Tubercle **11** 299, 1930

Lepers and nonlepers were tested with various dilutions of an extract in physiologic solution of sodium chloride of a piece of leprosy skin rich in Hansen's bacillus, the extract being sterilized by autoclaving for an hour. There was a lower response of the nonleprosy groups to the extract as compared with that of lepers, and this is considered evidence against the probability of a latent factor of leprosy playing any considerable part in the high reactivity of "healthy" natives tested in South Africa. A tuberculous group gave no sign of being more reactive than a nontuberculous group of nonlepers.

H. J. CORPLER

SEROLOGIC RELATIONS OF YEASTLIKE FUNGI C. E. LIM and T. J. KUROTCH-
KIN, Nat. M. J., China **16** 338, 1930

In studying the serologic relations of yeastlike fungi the use of water-soluble substances in the fungi as antigens has been found to give good results.

HEALING OF NECROTIC LESIONS PRODUCED BY BCG VACCINE J ZEYLAND,
Ann de l'Inst Pasteur **45** 157, 1930

Necrotic lesions produced by BCG vaccine in heavy doses in animals have been noted by several authors. With such heavy masses, killed organisms will, of course, produce identical tubercles, with necrosis. A series of twenty-three rabbits was observed following injection of BCG directly into the kidney, for periods to twenty-six months. There appeared, first, necrosis around the wound, enclosing great masses of BCG, surrounded by polymorphonuclears, some phagocytic. In two weeks, a great necrotic area was surrounded by typical tuberculous tissue, well vascularized. In the second month, calcified areas appeared in the necrotic mass, and the surrounding tissue lost its specific appearance. After a year, various stages of healing obtained. The organisms were rare, the lesions, small. Finally, healing appeared virtually complete, with minor scar tissue. The benignity of the vaccine, even under these extreme conditions, seems assured.

M S MARSHALL

DIPHTHERIA IMMUNIZATION WITH ANATOXIN G RAMON, Ann de l'Inst Pasteur **45** 291, 1930

In an article reviewing the history of his diphtheria anatoxin since its first use in 1923, Ramon affirms that this product has been adequately demonstrated to be innocuous (at the time of writing over 7,000 liters had been distributed under his supervision). Its value parallels a function of the flocculating property with antitoxin. It will, properly used, immunize 94 to 98 per cent of those treated, as demonstrated by the Schick test. Immunized persons are demonstrably immune for over four years and probably much longer or for life. It may be injected with a sterile protein (as typhoid vaccine) to confer a superior immunity of long duration. Immunity is rapidly developed. The proper doses are 0.5 cc, 1 cc and 1.5 cc, given subcutaneously at intervals of three weeks and of fifteen days, respectively.

M S MARSHALL

THE ANTITOXIN CONTENT IN SERUM FOLLOWING IMMUNIZATION WITH DIPHTHERIA ANATOXIN G RAMON and ROBERT DEBREL, Ann de l'Inst Pasteur **45** 326, 1930

A negative reaction to the Schick test, indicating at least 0.033 Ehrlich unit of diphtheria antitoxin per cubic centimeter of serum, is insufficient to determine the antitoxin following immunization with anatoxin. Of one series of 105 children, the authors found 40.9 per cent showing over one unit per cubic centimeter, 49.2 per cent over 0.1 unit, 5.7 per cent over 0.033 unit and 3.8 per cent less than 0.033 unit. Either two or three injections seemed to vary these results relatively little. Figures indicate more antitoxin in older immunized children than in infants, but the evidence is based on few cases. Perhaps the most interesting group considered is a series part of which was immunized in 1925, part in 1926, part in 1927 and part in 1928. The antitoxin content varied from over 1 unit per cubic centimeter (44 per cent of the four year group) down. The percentages are not statistically significant, but a good immunity seems assured in most cases, and one of great stability for some years, at least.

M S MARSHALL

THE CONSTITUTION OF TOXIN AND ANTITOXIN AND THEIR MODE OF UNION S SCHMIDT, Ann de l'Inst Pasteur **45** 337, 1930

The theories of physical or chemical union of toxin and antitoxin are discussed at length, following the school of Arrhenius and Madsen, particularly relative to the Ramon flocculation reaction. Essentially a review of some of the work during recent years, matters of rapidity, stability, reversibility, and avidity in flocculation are considered relative to their theoretical interpretation. No new work is presented, and no conclusions are drawn.

M S MARSHALL

ATTEMPTS TO INFLUENCE SPONTANEOUS TUBERCULOSIS IN RHESUS MACACUS
BY PERORAL ADMINISTRATION OF BCG A NOHLEN, Beitr z Klin d
Tuberk **74** 532, 1930

Seven monkeys each received perorally 5 mg of virulent human tubercle bacilli twice at an interval of forty-eight hours. In all the animals progressive tuberculosis developed, which in six of them produced definitely open foci. Seven other animals each received perorally, three times, 0.05 Gm of Calmette-Guerin bacilli. Thirty-three days later these animals were brought in contact with seven normal controls and with the seven infected animals. In five of these experiments the vaccinated animals showed no protective action of BCG, with the exception of a slight increase in their survival time. In one experiment both the normal control and the vaccinated animal remained healthy, in one experiment tuberculosis developed in the control, while the vaccinated animal remained healthy. The vaccination with BCG produced no untoward results.

MAX PINNLR

TUBERCULOUS REINFECTION AND ITS RELATION TO ALLERGY AND IMMUNITY
E A SCHNIGER, Beitr z Klin d Tuberk **74** 583, 1930

The bearers of healed tuberculous foci remain allergic for a certain period following the healing.

MAX PINNLR

FORMATION OF AGGLUTININ ON INTRACUTANEOUS INJECTION OF PARATYPHOID
B J SZEP, Ztschr f Immunitätsforsch u exper Therap **68** 274, 1930

The intracutaneous injection of emulsion of *B paratyphosus* B causes in rabbits much greater production of agglutinin than the subcutaneous injection of the same amount of the emulsion.

TITERS OF ISO-AGGLUTININS IN TUBERCULOSIS H ZANTOP, Ztschr f
Immunitätsforsch u exper Therap **68** 277, 1930

On careful comparison of available results there appears to be no noteworthy change in the titers of the iso-agglutinins in tuberculous patients.

IMMUNITY AGAINST PYOGENIC ORGANISMS ALFRED PETERSON, Ztschr f
Immunitätsforsch u exper Therap **68** 304, 1930

The antibacterial agency providing resistance against pyogenic infections with *Staphylococcus* and *Bacillus pyogenes* is not the bactericidal substances of the fluids of the body, but the polymorphonuclear leukocytes.

AMINES AS ANTIGENS Z JIRMOLJEWA and I BUJANOUSKAJA, Ztschr f
Immunitätsforsch u exper Therap **68** 342, 1930

A series of amines (trimethylamine, heptylamine, heptodezylamine) gave precipitation and fixation with homologous antisera.

THE ORIGIN OF COMPLEMENT E FRIEDBERGER and J GURWITZ, Ztschr f
Immunitätsforsch u exper Therap **68** 351, 1930

In the course of a study of the immune properties of normal serum it was found that complement is present in the serum of newly born guinea-pigs to about the same extent as in the mother. The complement makes its appearance in the serum in the very last stages of fetal life.

EFFECT OF BCG VACCINATION OF NEW-BORN GUINEA-PIGS BY MOUTH A I
TOGUNOWA and M M LARIONOWA, Ztschr f Tuberk **57** 312, 1930

Within the first few days after birth guinea-pigs received from 3.75 to 15 mg of Calmette-Guerin bacilli by mouth. They developed normally. After from one to two months about half of the animals had a temporary weak tuberculin allergy. Calmette-Guerin bacilli were demonstrable in the cervical and mesenteric lymph nodes and in the liver, and they were resorbed within the first few days after the administration. None of the animals showed lesions of progressive tuberculosis. The vaccinated animals had no definitely demonstrable immunity to a definitely virulent reinfection.

MAN PINNER

REACTION IN EXPERIMENTAL TUBERCULOUS REINFECTION E A SCHNIEDER,
Ztschr f Tuberk **58** 33, 1930

Rabbits were infected in the cornea with Calmette-Guérin bacilli and reinfected with minimal amounts of virulent bovine bacilli from 280 to 290 days after the first infection. The reinfected tissue was expelled in toto, leaving a round clean cavity in the cornea. The author believes that this phenomenon is essentially the same as that which leads to the formation of the round early cavities following an early infiltration.

MAN PINNER

THE EOSINOPHIL LEUKOCYTES IN IMMUNIZATION OF HORSES WITH DIPHTHERIA
TOXIN I FREUCHEN, Acta path et microbiol Scandinav (supp 3), p 123,
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The number of eosinophil leukocytes falls off as diphtheria toxin is injected and as the antitoxin in the blood increases in amount. As the antitoxin decreases, the number of eosinophils increases. The variations in the number of eosinophils are greater than the variations in the numbers of all the leukocytes and go in a contrary direction. The course of the eosinophils is similar to that in the majority of infectious diseases.

Tumors

EFFECT OF DYES ON THE VIRUS OF CHICKEN TUMOR NO 1 MARGARET REED
LEWIS, Am J Hyg **12** 288, 1930

The causative agent of the chicken tumor no 1 may be inactivated in the tumor extract by a number of the common biologic dyes. Some of these dyes brought about an unfavorable hydrogen-ion concentration in the solution containing the virus. Of those that did not produce an unfavorable hydrogen-ion concentration, toluidin blue, eosin, erythrosin, phenol indophenol, and dichlorophenol indophenol exhibited great inactivating power on the virus. Toluidin blue inactivated the virus of the chicken sarcoma in solutions containing about one part of dye to 10,000 parts of a highly virulent tumor extract.

AUTHOR'S SUMMARY

CARCINOMA OF THE FEMALE GENITAL TRACT IN CHILDHOOD A H MORSE,
Am J Obst & Gynec **19** 520, 1930

The literature contains a single record each of carcinoma of the vulva and carcinoma of the vagina, and eight records of a growth involving the uterus, in early childhood. A case is reported of a child, 10 years of age, who for two years had had a vaginal discharge followed by bleeding. Necrotic bits of tissue passed during an examination proved to come from an inoperable adenocarcinoma of the cervix.

A J KOBAK

HEMANGIOMA OF THE PELVIC CONNECTIVE TISSUE ROBERT T FRANK, Am J Obst & Gynec **20** 81, 1930

In an unmarried woman, 35 years old, a pelvic mass that reached the level of the navel on the right side and appeared to be continuous with the uterus was removed with great difficulty. It was vascular, cystic and edematous, and had many adhesions. The tissue was a simple hemangioma the septums of which consisted of loose, edematous, fibrillar connective tissue. The origin of the structure, which showed no intimate relationship with either uterus, adnexa, intestines or bladder, was apparently from the pelvic connective tissue. Six years previously a similar tumor had been removed from the left broad ligament. Two years after the second removal there was a third recurrence, which seemed to be arrested by radium. The author failed to find in the literature any report of a similar hemangioma of the pelvic connective tissue.

A J KOBAR

CHORIOEPITHELIOMA, WITH SPECIAL REFERENCE TO DISAPPEARANCE OF THE PRIMARY UTERINE TUMOR EMIL NOVAK and A K KOFF, Am J Obst & Gynec **20** 153, 1930

The authors classify trophoblastic tumors as benign or malignant chorionomas, the former include the benign hydatidiform mole, and the latter take up Ewing's group of chorio-epitheliomas. A report is made of a white woman, 35 years old, in whom, following a curettage for "retained tissue following abortion," metastatic growths developed in the lungs and brain, which proved to be chorio-epithelioma, while the uterus failed to show any primary tumor. Further study of the slide with the original curettings showed syncytium and Langhans' cells with definite malignant characteristics, such as mitosis and hyperchromatosis. Other cases of this type recorded in the literature are cited, and the explanations offered for the disappearance of the uterine tumor are reviewed.

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TUBERCULOSIS AND CANCER W C HULPER, Am Rev Tuberc **22** 271, 1930

The doctrine of an antagonism between active tuberculosis and cancer is supported by numerous and reliable experimental and statistical data, and has by far more evidence in its favor than any other conception of this matter. No definite conclusions can be drawn from the material available concerning the causative mechanism of this phenomenon, because reliable and extensive investigations into the effect of primary constitutional, secondary reactive and secondary mechanical factors of tuberculosis on the malignant growth do not exist. A direct toxic effect of tubercle bacilli on the cancer cells appears to be improbable.

H J CORPER

MULTIPLE GLIOMAS OF THE BRAIN KIYOSHI HOSOI, Arch Neurol & Psychiat **24** 311, 1930

In Hosoi's patient, a man aged 44, two days following an automobile accident trouble with speech developed (he could not pronounce words well) which grew steadily worse. He also vomited repeatedly, became incontinent and unsteady on his feet, and a right-sided hemiplegia developed. A few months before the accident, the patient had queer feelings and fears that he might lose his mind, but otherwise he was never sick. Neurologic examination revealed paralysis of the lower branch of the right facial nerve, hypo-active tendon reflex, fair voluntary movements in the extremities, a Kernig and a bilateral Babinski sign. The ankle jerks were absent. The pupils reacted normally, and the fundi showed congested retinal veins. As a glioma was suspected, a subtemporal decompression was done. An inoperable subcortical tumor was located in the left motor area.

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MULTIPLE GLIOMAS OF THE BRAIN KIYOSHI HOSOI, Arch Neurol & Psychiat **24** 311, 1930

In Hosoi's patient, a man aged 44, two days following an automobile accident trouble with speech developed (he could not pronounce words well) which grew steadily worse. He also vomited repeatedly, became incontinent and unsteady on his feet, and a right-sided hemiplegia developed. A few months before the accident, the patient had queer feelings and fears that he might lose his mind, but otherwise he was never sick. Neurologic examination revealed paralysis of the lower branch of the right facial nerve, hypo-active tendon reflex, fair voluntary movements in the extremities, a Kernig and a bilateral Babinski sign. The ankle jerks were absent. The pupils reacted normally, and the fundi showed congested retinal veins. As a glioma was suspected, a subtemporal decompression was done. An inoperable subcortical tumor was located in the left motor area.

Necropsy, which was performed one-half hour after death revealed one hemorrhagic glioma under the rostrum of the corpus callosum involving the right more than the left hemisphere, a similar tumor over the left motor area extending into the corona radiata and a third, smaller tumor in the left putamen. Microscopically the gliomas were generally of the astrocytic variety, but in some places showed a more diversified structure. Hosoi considers the three tumors of independent, multicentric, not metastatic origin.

G B HASSIN

GANGLIOGLIOMA CYRIL B COURVILLE, Arch Neurol & Psychiat **24** 439, 1930

Ganglioglioma is a tumor made up of ganglion and glia elements. In these tumors the cells are fairly advanced in their differentiation, the adult forms being rather conspicuous. After reviewing eighteen cases from the literature, Courville describes two cases of his own. In one, the tumor was in a girl, aged 15, and arose from the tuber cinereum. At the age of 4 the child became idiotic, blind, hydrocephalic, and completely paralyzed on both sides. After a cyst in the left parietal lobe was evacuated, the patient recovered "almost completely," but within a year the condition became worse again. Another operation, with the removal of the cyst, improved the child's mental condition, but blindness developed in the right eye and the right side of the body became paralyzed. At the age of 15, after an injury, convulsions developed followed by death. Necropsy revealed a suprasellar tumor, 3.5 cm long and about 1.5 cm in diameter, and a cyst in the left hemisphere, 9 by 6 by 7 cm, which contained in its anteromedian aspect a small tumor which was continuous with the previous tumor mass. Both lateral ventricles were dilated, the structures of the basal ganglions were distorted, and in some instances was unrecognizable. Specific staining methods (Cajal, Schultze-Stohr) showed neuroblasts without or with processes, well developed ganglion cells usually in a state of degeneration and nerve fibers which were all unmyelinated and often varicose. In addition there were spongioblasts, unipolar, bipolar and fully developed and astrocytes (in the wall of the cyst only). A reticular network of glia fibers could be demonstrated with the methods of Mallory and Alzheimer. Blood vessels were numerous, they were infiltrated with lymphocytic elements and represented the connective tissue of the tumor masses. Fat was present in the form of minute granules. The main components of the tumor were ganglion and glial cells—a ganglioglioma of the tuber cinereum—"the fifth case to be reported in this location."

In the second case, with no history, a tumor from 1 to 2 mm in diameter was found in the tuber cinereum behind and to the left of the infundibulum. It was cellular, ganglion and glia cells and probably neuroblasts were embedded in a loose stroma, glia fibers were numerous and with the rich capillary network formed the larger part of the intercellular substance.

Of the numerous names given such tumors (ganglionic neuroma, neuroganglioma, neuroglioma, ganglioneuroma, ganglioglia-neuroma and ganglionic glioma) Courville prefers the term ganglioglioma because the tumors contain both ganglion cells and neuroglia. In the tuber cinereum this type of tumor most likely arises in the indifferent cells of the basal plate of the diencephalon.

G B HASSIN

SYSTEMIC INFLUENCES IN IMMUNITY AND CANCER ARTHUR EASTWOOD, J Hyg **30** 267, 1930

The idea that there are systemic influences concerned with the genesis of cancer has assumed many forms and is often expressed ambiguously. Does it mean that normal cells have a "natural tendency" to malignant growth and actually become malignant if freed from systemic control? I do not accept this "natural tendency" unrestrained growth does not suffice to explain the origin of cancer. What is meant by "systemic control"? My view is that such control regulates normal cells,

and that cancer cells are independent of it, I do not agree that there is a special kind of antimalignant systemic control that may destroy the fully fledged cancer cell. What is the nature of "susceptibility" to the change into the cancerous condition? I regard it as essentially a cellular property, not as a humoral or systemic influence though I admit that irritant material that gains access to the circulation may increase the susceptibility of particular cells. What is meant by "resistance" (either local or systemic) to cancer? Owing to the recuperative powers of the animal body, local disturbances of metabolism are often corrected, and there is a return to the normal condition, some of these disturbances, if left uncorrected, might lead to cancer, and the fact that they are corrected may, if one likes, be called resistance to the genesis of cancer. It is also known that true cancerous foci or metastases may remain quiescent for a considerable time, but I do not agree that such quiescence has been shown to be attributable to a specific kind of antimalignant "resistance" (either local or systemic).

While there is no satisfactory evidence, either direct or indirect, of a systemic influence that causes cancer, systemic influences are so complex and obscure that this possibility cannot be definitely excluded. But there does not seem to be any cogent reason for dissenting from the view that the production of the malignant variant is due to its local environment.

AUTHOR'S SUMMARY

EXTRACT OF ADRENAL CORTEX AND CANCER S. ITAMI and E. McDONALD, Science **72** 460, 1930

Spontaneous carcinoma of the breast in the mouse was treated by the extract of adrenal cortex of Swingle and Pfiffner, without any curative or restraining effect on the tumor. No therapeutic value in the treatment for such cancers in animals was shown in the cortical hormone, although the efficacy of this preparation in substituting for the adrenal cortex hormone in adrenalectomized animals has been thoroughly proved. The use of such extract of adrenal cortex in human patients is therefore not to be recommended as a treatment for cancer, but this in no way detracts from the value of this extract of adrenal cortex of Swingle and Pfiffner in conditions other than cancer, as it has been proved to be effective as a substitute for the cortical hormone.

AUTHORS' CONCLUSIONS

TUMORS OF THE PAROTID GLAND E. B. BENEDICT and J. V. MEIGS Surg Gynec Obst **51** 626, 1930

Study of eighty cases of tumors of the parotid gland showed that a mixed tumor grows slowly but occasionally increases in size rapidly because of superimposed sarcomatous or carcinomatous changes and commonly recurs after excision. Carcinoma was diagnosed in thirty of the patients, in whom metastases were present in the lungs, bones and skin. In nine sarcoma was diagnosed. In seven the gland was secondarily invaded by carcinoma, melanotic sarcoma and malignant lymphoma. Nothing new is added to the classification of Ewing.

RICHARD A. LIFVENDAHL

PRIMARY CARCINOMA OF THE FALLOPIAN TUBES W. W. HOLLAND, Surg Gynec Obst **51** 683, 1930

Primary carcinoma of the fallopian tubes was found in 9 of 10,000 cases of completely removed tubes, in 70 cases the tubes were secondarily involved from carcinoma of the uterus or ovary. In 1 case bilateral carcinoma was associated with tuberculosis. From the examination of these tubes it appears that inflammatory changes do not deserve the etiologic significance in carcinoma attributed to them by many writers.

RICHARD A. LIFVENDAHL

THE USE OF HEPARIN PLASMA FOR THE GRAFTING OF SPONTANEOUS MAMMALIAN TUMOURS INTO HOMOLOGOUS ANIMALS M J A DLS LIGNERIS,
Brit J Exper Path **11** 249, 1930

In a case of melanoma in an Angora goat, grafting which had previously failed was successful when heparin-treated goat plasma was used as a nutritive and protective medium surrounding the transplanted particles of tumor

AUTHOR'S SUMMARY

VENOUS INVASION IN METASTATIC TUMORS IN THE LIVER RUPERT A WILLIS
J Path & Bact **33** 849, 1930

From a series of 120 consecutive autopsies in cases of malignant disease, 12 are selected to exemplify the importance of malignant penetration of the afferent and efferent veins of the liver in the metastatic spread of tumors to and from that viscus. Invasion of the larger tributary portal vessels or of the portal vein itself by neoplasms, primary or secondary, in the portal drainage area is a potent factor in producing widespread multiple hepatic metastases by portal embolism. Established hepatic growths whether primary or metastatic, and of the latter whether sown in the liver by the portal or arterial blood, frequently penetrate adjacent branches of the portal system and produce corresponding regional broods of further metastases in the liver. These factors alone or combined are responsible for the familiar bulky liver thickly studded with secondary growths. Invasion of the efferent veins of the liver by intrahepatic growths is an important factor in further metastatic dissemination to the lungs. Penetration of the inferior vena cava itself may occur.

AUTHOR'S SUMMARY

SACRAL CHORDOMA WITH WIDESPREAD METASTASES RUPERT A WILLIS, J
Path & Bact **33** 1035, 1930

An unusual malignant sacral chordoma is recorded which presented the following features: the primary tumor was one of the largest, if not actually the largest, so far described, prolific remote metastases, probably due to tumor invasion of the iliac veins, were present in the lungs, the heart, the liver, the spleen, the kidneys, the thyroid gland and the skin, the patient also presented numerous exostoses of many bones, the possibility that these and the chordal tumor may both be expressions of a constitutional tendency to skeletal anomalies is discussed.

AUTHOR'S SUMMARY

A PULMONARY NEOPLASM SIMULATING TUBERCULOSIS IN ADOLESCENCE D P
SUTHERLAND and J R BEAL Tubercle **11** 529, 1930

An interesting case of primary carcinoma of the lung in a patient 17 years of age is reported—an extremely rare condition. The atypical symptoms to which the growth gave rise, and more especially an obstruction of the common bile duct due to a pancreatic stoppage, are regarded as unusual in carcinoma of the lung. The history, clinical examination and roentgen appearances pointed to pulmonary tuberculosis. Only when signs of pressure, such as obstruction to the biliary passages, began to appear did the diagnosis of neoplasm of the lung suggest itself.

H J CORPER

THE MICROSCOPIC STRUCTURE OF GIANT CELL EPULIS I WAILGREN, Arb
a d path Inst zu Helsingfors **6** 21, 1930

Extensive studies are reported on the various elements comprising a giant cell epulis. The small cells which make up the bulk of this tumor are connected with one another by cell processes, and apparently are the predecessors of giant cells, although the origin of these giant cells from the endothelium of blood vessels is

admitted Subcutaneous bone transplants in guinea-pigs were used to corroborate observations on numerous tumors The results of the studies seem to justify the assumption that epulis is not granulation tissue, but a presarcomatous mass Cell measurements, especially on nuclei and nucleoli, form the basis for the majority of the opinions expressed

GEORGE RUKSTINAT

THE CELI STRUCTURE OF EPITHELIAL TUMORS OF THE MAMMARY GLAND
A KLOSSNER, Arb a d path Inst zu Helsingfors 6 81, 1930

In order to eliminate any possible confusion, the breast was studied in various phases of menstruation, no characteristic alterations in the cells were observed It was found that in benign tumors, such as adenomas and fibro-adenomas, the cell structure remained normal, but in carcinoma the cells were definitely altered The alterations were especially evident in the nuclei and the centrosomes Also, in cancer cells, three or four centrioles occurred instead of the normal two

GEORGE RUKSTINAT

Salivary Stone with Formation of Carcinoma at the Base of the Tongue
R BAYER, Centralbl f allg Path u path Anat 49 102, 1930

Embedded in a squamous cell carcinoma of the right side of the tongue, a salivary calculus, the size of a hazel nut, was found There were metastases of the carcinoma to the regional lymph glands When found in the midline, such stones usually arise in remnants of the thyroglossal duct Bayer thinks the lateral position of the stone in his patient indicates an origin in one of the small salivary glands

GEORGE RUKSTINAT

Malignant Melanotic Tumors of the Nail Bed on a Traumatic Basis
W SCHOPPER, Centralbl f allg Path u path Anat 49 195, 1930

Malignant melanotic tumor of the thumb nail bed after trauma in two men is reported In each instance the tumor developed about a year after the trauma, and was situated in tissue which was the site of chronic inflammation In one instance the tumor metastasized to the axillary lymph glands Evidence of preceding pigmented nevus, the usual source of such tumors, was lacking

GEORGE RUKSTINAT

Adenoma of the Parathyroid
M ZAJI WLOSCHIN, Frankfurt Ztschr f Path 40 132, 1930

After a short review of the literature, the author describes a tumor of the right parathyroid gland in a man 57 years old The tumor was well separated from the thyroid gland It measured 13 by 3 by 43 cm, and was of firm consistency One portion showed a small cyst filled with clear liquid Histologically, the tumor consisted of epithelial cells showing a netlike arrangement similar to that in the normal parathyroid gland The cells varied in shape and size In some portions, small lobules consisting of similar cells were recognizable In other portions, small bands of connective tissue surrounded by groups of cells in palisade-like arrangement could be demonstrated by the van Gieson stain Some of the cells showed their membranes very indistinctly, giving the impression of syncytial masses Neither colloid nor follicles nor oxyphil cells were demonstrable The author is of the opinion that the tumor was an actual new growth, rather than evidence of hyperplasia of the parathyroid gland

O SAPIIR

MULTIPLE LEIOMYOMA SARCOMATODES OF THE STOMACH
A ANTONOW, Frankfurt Ztschr f Path 40 173, 1930

In a 21 year old woman who complained of gastric distress, multiple tumor nodules were found in the stomach during operation The stomach, a few enlarged lymph nodes of the omentum and the gastrocolic ligament were resected The

tumor nodules were found throughout the different layers of the stomach. Neither the serous surface nor the mucosa in the region of the nodules showed interruption of their continuity. Some of the nodules showed a few cysts, the walls of which were formed by broken-down tumor tissue. Histologically, the tumor consisted of immature muscle elements. Many cells were markedly vacuolated, their nuclei pushed over toward the peripheries of the cells. Some portions showed cells with oval or round nuclei and a hardly recognizable cytoplasm. Other sections contained many oval cells arranged in groups. Some of these groups were separated from one another by masses of erythrocytes located close to blood vessels. In other portions, oblong and spindle-shaped cells were present, many of which showed rounded edges. These cells were arranged in bundles extending in various directions. An invasion by many tumor cells into surrounding structures was noted. Many vascular slits were found. The lymph nodes showed an invasion by similar tumor cells. By the use of the Foot and Menard stain for reticulum, many reticulum fibers were demonstrated throughout the tumor. The author believes that the occurrence of multiple tumor nodules throughout the stomach in this case tends to support Conheim's and Fischer-Wasel's theories as to the origin of tumors.

O SAPHIR

PRECURSORY CHANGES TO CANCER IN THE ESOPHAGUS H. SCHÄER, *Ztschr. f. Krebsforsch.* **31** 217, 1930

Systematic studies were made of the esophagus of 237 persons over 40 years of age. Leukoplakia was found with some frequency in 67 per cent of the cases and does not appear to play the important role in the development of cancer in the esophagus that it does in the development of cancer in the mouth. Varying degrees of chronic esophagitis were found with about the same frequency, but no parallelism could be found between this and epithelial hyperplasia. Traction diverticula were found in 12 patients more frequently in men, as was the case with leukoplakia. These were often associated with epithelial overgrowths, and Schäer regards them as playing an important part in the causation of cancer. In one patient an atypical epithelial growth was also observed in a small ulceration of the mucosa, either an unhealed peptic ulcer of the esophagus or an ulcerated diverticulum.

H. E. EGGERS

FIVE HUNDRED CASES OF GASTRIC CANCER I. POSCHARISKY, *Ztschr. f. Krebsforsch.* **31** 263, 1930

A study of the autopsy protocols of 500 cases of gastric cancer is reported, with the following conclusions. Malignancy expressed in terms of dissemination is in part the function of age, in that metastasis is more frequent at earlier ages, in part, the morphologic character of the tumor, the more atypical ones showing the most constant tendency toward dissemination, and in part, the location of the primary tumor since metastasis is more frequently lacking in carcinomas of the pylorus and increasingly frequent in the case of those of the cardia, fundus and pyloric antrum.

H. E. EGGERS

THE SYMPTOMATOLOGY OF PRIMARY BRONCHIAL CANCER C. KUHN, *Ztschr. f. Krebsforsch.* **31** 276, 1930

At the city hospital of New Cologne it was found in autopsies performed in all cases of cancer that in the five year periods since 1900 there has been an increase in the incidence of primary bronchial carcinoma, from 4.68 to 10.63 per cent. It was more frequent in men than in women, the ratio being 5.059, and occurred most often in the sixth and seventh decades of life. The usual primary sites were the right lung and the upper lobes of the lungs. An exudative pleuritis was present in 18 per cent of the cases, the exudate showing a predominance of

lymphocytes with some polymorphonuclears. Metastases were most usual in the liver, regional lymph glands, kidneys, bones, suprarenal glands and pleura and in the lung itself. No relationship was evident to tuberculosis, occupation or the specific irritative element.

H. E. EGGERS

MULTIPLE PRIMARY CARCINOMAS AND THEIR FREQUENCY. R. F. MULLER, *Ztschr. f. Krebsforsch.* **31** 339, 1930.

Among the 1,121 cases of cancer coming to autopsy at the Allgemeinen Krankenhaus St. Georg at Hamburg during the last four years there were 21 cases of multiple primary carcinoma. Basing his calculations on the incidence of cancer in proportion to the cause of other deaths at that institution, Muller estimates the theoretical incidence of such cases as 18—a close approximation to that actually observed, and indicating both a lack of atreptic immunity and of special predisposition. Among the curiosities of this series, there were observed an instance of the metastasis of one carcinoma, an epithelioma of the tongue, in another, a carcinoma of the lung, and a colliding growth of a carcinoma of the lung with an esophageal carcinoma.

H. E. EGGERS

TESTICULAR TUBULAR ADENOMA OF OVARY. O. BERNER, *Norsk mag. f. lægevidensk.* **91** 1177, 1930.

In a woman, aged 22, with increasing symptoms and signs of hermaphroditism a round, firm, whitish tumor almost the size of a fist, was found in the right ovary. The tumor, covered by a capsule of connective tissue, was doughlike, and its surface smooth, except in the region of the hilus. Cross-section showed a peculiar yellow color. The tumor consisted of numerous sharply defined lobes separated by connective tissue containing fairly many and large blood vessels. In most of the lobes were numerous tubules, sometimes with compact masses of epithelium. In the intertubular connective tissue were large protoplasmic cells, each with a large bladder-shaped nucleus and distinct nucleoli. These cells, strongly resembling Leydig's cells of the testicle, contained fat in sudan-stained sections. Ovarian tissue was present in the capsule, especially in the thicker portion, which rested almost like a hood over the testicular part of the tumor. Four weeks after the operation normal menstruation occurred, and a gradual disappearance of hirsutism followed. A half year later nothing abnormal in the patient's body was observed apart from some enlargement of the clitoris. Berner states that, with Popoff's case (*ARCH. PATH.* **9** 31, 1930), this is the sixth case of testicular tubular adenoma of the ovary in the literature. It shows a remarkable similarity to the cases of Pick, Schickele, Neumann and Strassmann. The article is accompanied by photographs and a drawing in color.

Medicolegal Pathology

GAS BACILLUS INFECTION OF THE BRAIN DEVELOPING THIRTEEN YEARS AFTER GUNSHOT INJURY. H. DURCK, *Beitr. z. path. Anat. u. z. allg. Path.* **84** 667, 1930.

Durck reports a case that he interprets as one of unusual latency of infection with the gas bacillus. The patient was a 34 year old criminal who was transferred from prison to the hospital in extremis. Eight days previously he had begun to feel ill, and two days before death he had what was described as a stroke of apoplexy. On his admission to the hospital the left side of his body was paralyzed. At necropsy there was found an abscess of the right cerebral hemisphere. The abscess contained gas and Welch-Fraenkel bacilli. In 1916, while in the army, the man had sustained a severe gunshot injury of the right side of the head. Durck believes that the infecting organisms were introduced into the brain at this time and lay dormant until activated by some unknown cause thirteen years later.

O. T. SCHULTZ

COLPOSCOPIC DETECTION OF CRIMINAL ABORTION HANS HINSELMANN,
Deutsche Ztschr f d ges gerichtl Med **16** 14, 1930

Colposcopic examinations are urged for all cases in which criminal abortion is suspected, since definite or characteristic changes in the cervix uteri, such as instrumental injuries, scar, etc., may be found during life. This fact is well illustrated by two cases

E. L. MILOSLAVICH

DEATH BY BURNING L. WACHHOLZ, Deutsche Ztschr f d ges gerichtl Med
16 18, 1930

This is a medicolegal analysis of accidental, suicidal and homicidal deaths by burning. Suicide by burning seems to be more frequent than generally is assumed. Fourteen cases of suicidal burning are reported, twelve involving women, and two, men. Four of the women were insane, the other eight, among them two prostitutes, committed suicide by burning after passionate quarrels with lover or husband. The two men, sufferers from alcoholism, committed the act while intoxicated. In instances of suicide, the body is found, as a rule, in a prone position, as the person tries to protect his face from the flames. Three cases of murder by burning are presented in an interesting manner and the circumstances analyzed.

E. L. MILOSLAVICH

GLIOMA AND TRAUMA OTTO BECKMANN, Deutsche Ztschr f d ges gerichtl
Med **16** 26, 1930

To establish a direct relation between tumor of the brain and injury, one must carefully consider the following important criteria: 1. The injury to the skull must affect the brain or the meninges. 2. Symptoms of the injury must be evident during life and proved at autopsy. 3. A certain interval of time should elapse between the trauma and the occurrence of the tumor. 4. The tumor should be found at the site of the injury or in the direction of the coup-contrecoup action. 5. The character of the growth should be determined microscopically. Five cases are presented, and the literature on this subject is discussed.

E. L. MILOSLAVICH

Technical

DIFFERENTIAL WHITE COUNT IN INFANCY CARL H. SMITH, Am J Dis Child
40 505, 1930

The differential blood count of thirty-seven normal and sick infants was studied from a supravital preparation and from fixed smears, and the observations were correlated. In forty-three of forty-eight comparative smears, the percentage of polymorphonuclear leukocytes was higher, and that of lymphocytes was lower in the living preparation than in the fixed film. The average of twenty-four counts from the group of normal infants showed the percentage of polymorphonuclear neutrophils to be 86 per cent higher in the supravital than in the fixed coverslip smear and almost 12 per cent higher than in the slide. The lymphocytes, on the other hand, ran 14 per cent and 11 per cent higher in the fixed smear of the slide and coverslip, respectively, than the corresponding cells of the supravital preparation. The principal reasons for this discrepancy are the unequal distribution of the cells and, especially, the failure to identify and include all fragmented polymorphonuclear leukocytes in the differential count of the fixed smear. With the supravital technic, the spread of cells is more even, trauma is reduced, and both motile and dying cells may be more readily identified. The lymphocyte has always been regarded as the predominant cell in the blood of the infant. This

observation has heretofore been based on differential counts employing the fixed smear with some modification of the Romanowski stain. While counts made from the supravital film confirm the preponderance of lymphocytes over polymorphonuclear leukocytes, it is often by no means as marked as indicated in the fixed smear. The differential count from the fixed smear may unduly exaggerate the lymphocytic percentage and convey an erroneous impression of a blood dyscrasia. In pyogenic infections, especially when associated with a leukocytosis, the differential count from the fixed smears gives at times a much lower polymorphonuclear and a higher lymphocyte percentage than expected. That this discrepancy is often due to an increased fragility of the polymorphonuclear leukocytes is evident from comparative supravital studies. In a routine differential count from the fixed smear, particularly when it is employed as an index of the patient's resistance, the extent of damage to the white cell encountered on the slide should be noted. If fragmented cells have been included in determining the individual cell percentage, mention of this fact should also be made.

AUTHOR'S SUMMARY

THE COSTA REACTION HARRY S. PIAN, *Am Rev Tuberc* **21** 684, 1930

The Costa reaction is essentially a nonspecific reaction. Three minims of 5 per cent sodium citrate are mixed with 15 cc of 2 per cent solution of procaine. To this are added 3 minims of the patient's blood. This is either centrifugated or allowed to settle for twenty-four hours. Then 1 minim of concentrated formaldehyde solution is added, and the results recorded according to the degree of cloudiness and the time required for its appearance. A heavy flocculation appearing in from one-half to one minute is rated +++++. The absence of, or only faint, cloudiness after eight minutes is said to be negative. As the result of the examination of 130 cases, the Costa reaction is considered a valuable aid in determining activity in tuberculosis, but cannot be used to determine the degree of activity.

H. J. CORPER

RED BLOOD CELL SIZE IN ANEMIA WILLIAM P. MURPHY and GRETHER FITZHUGH *Arch Int Med* **46** 440, 1930

The determination of the volume of the individual cells as suggested by Haden and as herein recorded is a more simple means of determining the average size of cells than is the measurement of their mean diameter. Determinations of the volume of the individual cells are helpful in differentiating pernicious anemia from other anemias in most instances in which difficulty in diagnosis might arise, the outstanding exception being in the rare condition of so-called aleukemic leukemia. During and shortly following acute loss of blood, there is an increase in the average volume of the individual cells, whereas in anemia resulting from chronic loss of blood, it is generally low. Figures presented suggest that with the adequate administration of liver, the red blood cells of patients with pernicious anemia return to normal volume. A figure for the volume of individual cells greater than normal should indicate inadequate treatment. Not only is the method for determining the volume of the individual cells a simple one to use, but the information so obtained is also as reliable as is that obtained by measurement of the mean diameter of the red blood cells by the method used.

AUTHORS' SUMMARY

STAINING NERVE FIBERS IN MOUNTED SECTIONS WITH ALCOHOLIC SILVER NITRATE SOLUTION H. A. DAVENPORT, *Arch Neurol & Psychiat*, **24** 690, 1930

Davenport describes his new method of staining celloidin or paraffin sections with silver. The former are mounted on slides with albumin fixative and plunged immediately into a 2 per cent solution of celloidin. When the edges of the original celloidin soften, the slide is removed, drained quickly, inverted and tilted back and forth, and laid face up until the coating sets. Before the drying of

the surface begins, the specimen is put into a solution of 80 per cent alcohol. After a few minutes it is ready for the silver bath—a solution of 10 per cent silver nitrate in 85 per cent ethyl alcohol slightly acidified with nitric acid (from 5 to 7 drops of a 7 per cent concentrated aqueous solution of nitric acid to 50 cc of the silver solution). The sections remain in the latter approximately one hour or longer until a light brown tint appears in the tissue. After removal from the silver bath, the section is rinsed quickly in strong alcohol (from 95 per cent to absolute) and reduced in an alcoholic solution of a mixture of formaldehyde and pyrogallol, the intensity of reduction is judged by the intensity of the brown color. Then the sections are passed through two or three changes of 95 per cent alcohol, absolute alcohol, xylene and Canada balsam (from 2 to 3 minutes each).

The mounted paraffin sections are treated in the same manner, but first they should be passed through xylene, absolute alcohol and alcohol-ether.

With the method outlined, Davenport demonstrated nerves and end-plates in the voluntary muscles of the cat and the nerves in the spinal cord of man and dog, however, the fibrils and synaptic end-loops could not always be demonstrated, while the finest fibers of the gray substance could not be demonstrated at all.

G B HASSIN

THE TAKATA-ARA COLLOIDAL TEST WITH SPINAL FLUID LOUIS J KARNOSH and HAROLD N KING, Arch Neurol & Psychiat **24** 743, 1930

The Takata-Ara's method—1 cc of spinal fluid plus 1 drop of 10 per cent solution of sodium carbonate solution, plus 0.3 cc of equal parts of a 0.5 per cent solution of corrosive sublimate and 0.02 per cent fuchsin solution—causes no changes in the color of a normal spinal fluid, the mixture remains clear and violet. In cases of tabes and dementia paralytica, it becomes cloudy and a precipitate forms. In meningitis the fluid becomes red.

In testing this method Karnosh and King compared the results they obtained with the colloidal reaction of the gum mastic. The cerebrospinal fluids tested were taken from patients with dementia paralytica, senile dementia, arteriosclerotic brain disease, alcoholic psychoses, manic depressive insanities, schizophrenia and various other psychoses and organic brain diseases. Altogether 180 cases were studied. The conclusions are that the test is not specific; it has no advantages over similar tests such as Weichbrodt's, it is positive in 82 per cent of the cases of so-called metasyphilis, and it is frequently positive in cases of arteriosclerosis, trauma or tumors of the brain.

G B HASSIN

THE USE OF ACID FUCHSIN IN RUSSELL'S TRIPIL SUGAR MEDIUM G D CUMMINGS, J Infect Dis **47** 359, 1930

The preparation of Andrade indicator as outlined in the literature is unnecessary, since undecolorized acid fuchsin may be used with equal success. Andrade indicator as generally prepared contains enough normal sodium hydroxide to decolorize the acid fuchsin present and to have a decided effect on the pH of the medium to which it is added. A 1 or 2 per cent concentration of aqueous acid fuchsin used in 1 per cent amounts in the Russell medium gives clearcut and correct reactions with the following five organisms when incubated for twenty-four hours at 37 C: *Eberthius typhosus* Rawlings, *Salmonella paratyphosus* A, *Salmonella paratyphosus* B, *Eberthella dysenteriae* Shiga, and *Escherichia coli-communior*. The finished medium has sufficient pink color to indicate the production of alkali. Undecolorized acid fuchsin is recommended for use in the Russell medium, because of its chemical stability, ease of preparation, ability to give clearcut reactions and lack of inhibitory effect. The use of undecolorized acid fuchsin for the preparation of Andrade indicator would eliminate the variety of methods now to be found in the literature.

AUTHOR'S SUMMARY

STAIN FOR RICKETTSIA BODIES M RUIZ CASIANEDA, J Infect Dis **47** 416, 1930

A buffer formaldehyde solution is prepared as follows *A* 23.86 Gm of sodium phosphate is dissolved in 1 liter of distilled water *B* 11.34 Gm of monopotassium phosphate is dissolved in 1 liter of distilled water Thirty-eight parts of *A* and 12 parts of *B* are mixed and filtered through a Berkefeld candle, 0.2 per cent of formaldehyde is added as a preservative The buffer solution should have a pH of 7.6 The stain is made as follows 20 cc of buffer solution, 1 cc of formaldehyde, 3 drops of Löffler's methylene blue (methylthionine chloride, U S P) or 10 drops of 1 per cent methylene blue Stain with this mixture for two or three minutes After washing the slide with running water for thirty seconds, the counterstaining is done with aqueous safran for one or two seconds

EDNA DEIVES

THE STAINING OF CALCIUM G R CAMERON, J Path & Bact **33** 929, 1930

Silver nitrate is not a test for calcium or phosphate, the black reaction is given by a variety of solid deposits of which the anion is more important than the metal Alizarin is a nearly specific stain for calcium It reacts readily in vitro and in vivo with recently deposited calcium phosphate or carbonate, normal or pathologic, but often fails to stain older deposits This limits its practical utility Hematoxylin does not stain calcium salts, although it often identifies areas in which changes favorable to the deposition of calcium salts are taking place The reaction obtained in these areas depends partly on the presence of iron and mostly on a peculiar ground substance which is normally present in bone and cartilage and which also appears at the site of pathologic calcification and, mordanted with aluminium or chromium stains deeply with hematoxylin

AUTHOR'S SUMMARY

ASCHHEIM-ZONDEK TEST G ANDRESSI, Clin obstet **32** 449, 1930

From the application of the Aschheim-Zondek test to forty-eight pregnant women, in various months of gestation, forty-seven positive results and one negative result were obtained Of eight women with extra-uterine pregnancies, six gave a positive reaction and two a negative reaction In sixteen puerperal women it was demonstrated that the hormone of the anterior lobe of the hypophysis is eliminated with relative rapidity, for after the sixth day following the birth the reaction was always negative In twenty-four women of various ages with various gynecologic disorders, healthy men of various ages and others employed as controls, the result of the test was always negative The importance and the utility of the test are emphasized, especially in those cases of initial pregnancy in which the clinical examination oftentimes does not furnish sure results

A NEW METHOD FOR THE EXAMINATION OF THE SMOOTH MUSCULATURE OF THE LUNG A LUISADA, Beitr z Klin d Tuberk **73** 657, 1930

A method is presented by which the contractions of the smooth musculature in the lung can be recorded by a method similar to that used in making an electrocardiogram Electrograms were recorded of animals under normal condition after the resection of the vagus nerve, after stimulation of the vagus and sympathetic nerves and under the influence of various drugs that act on the neuro-vegetative system During the anaphylactic shock, the contraction of the smooth musculature is constantly increased, and a lack of correlation exists between the smooth and striped respiratory musculature The method was elaborated in such a way that human electrobronchograms could be recorded One electrode is applied to the trachea and another to a small bronchus

MAX PINNER

PREVENTION OF THE FORMATION OF MOIDS IN KAISERLING II SOLUTION A
GAAL, *Centralbl f allg Path u path Anat* **49** 97, 1930

The addition of 15 cc of liquid carbolic acid to each liter of Kaiserling II solution prevented the formation of molds for at least three years There was no alteration of color in the specimens

GEORGE RUKSTINAT

A METHOD FOR THE SAMPLING OF ALVEOLAR AIR IN MAN M E MARSHAK,
Ztschr f d ges exper Med **72** 32, 1930

A method is described by which samples of alveolar air may be collected over mercury Samples collected by this method apparently contain a higher percentage of carbon dioxide than alveolar air collected over acidulated water

PEARL ZIEK

Society Transactions

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, Nov 19, 1930

LEILA CHARLTON KNOX, *President, in the Chair*

HEMORRHAGE INTO THE PERICARDIUM FOLLOWING RUPTURE OF A CORONARY ARTERY CHARLES T. OLCOTT

A specimen of a heart was presented in which there had been a rupture of the circumflex branch of the left coronary artery with resulting hemopericardium. There was no aneurysm. The patient was a man aged 60, who had previously been healthy. The symptoms suggested angina pectoris. There was an interval of fifteen hours between the first symptoms and death.

In a fairly complete review of the literature only thirty other cases were found in which the lesion was clearly due to coronary rupture, and in which the surrounding myocardium was normal. Sixteen cases were unassociated with aneurysm, while in fifteen aneurysm was found. The etiology seems to have been atheromatous in fourteen cases (ten without aneurysm), due to infectious embolism in five cases (four with aneurysm), and due to syphilis in two cases, both with aneurysm. Nineteen cases occurred in males, and eleven in females. The average age of the patients with atheromatous conditions was 65 years, of those with infectious embolism, 19.2, and of those with syphilis, 46. Rupture occurred in the left artery eleven times, in the right artery eight times and in both arteries three times.

This article will be published in full in *The New England Medical and Surgical Journal*.

DISCUSSION

HELEN S. PITTMAN (by invitation). We performed an autopsy on a Greek woman somewhat over 60, who came to St. Luke's Hospital about 6 a. m. and died before reaching the ward. She spoke very little English, as did the people who were with her, so that the history is incomplete. She had awakened at 1 o'clock that morning with severe pain in the upper part of the abdomen, with some radiation to both arms. She was examined while in a moribund condition, and died almost immediately. Autopsy was performed about three or four hours after death, and the pericardium was found distended with blood and fresh clots. There were three lacerations in the epicardium on the posterior surface of the tip of the left ventricle, and there was a diffusion of blood in the subepicardial tissue. When the left ventricle was cut open, it was seen that there was a fresh hemorrhagic infarct in the tip of the left ventricle, and the probe passed through the epicardium came out on the surface. There was extensive arteriosclerosis with calcification. The base of the mitral ring measured about 4 mm. across and was solidly calcified. Both coronary arteries were calcified throughout, and up to the present time no rupture of the vessel has been found. The heart is now being hardened for section.

CLARENCE DE LA CHAPELLE. I have seen three cases of ruptured coronary artery, two were from the service of the chief medical examiner, Charles Norris, and were from patients of unknown age. The age of one patient was guessed to be 55. He had syphilitic aortitis and an aneurysm of the left coronary artery near its origin, which had perforated through the wall of the left auricle. A man, whose age was guessed to be 60, had a rupture of the left circumflex branch about the

midportion, his arteries were markedly sclerotic. In both of these cases a history was not obtainable. The third case was a hospital case, a Negro, aged about 21 entered the hospital with signs of cerebral hemorrhage. At postmortem examination we found the cerebral hemorrhage, but we also found a ruptured descending branch of the left coronary artery. Marked hypoplasia of the aorta and other signs of status lymphaticus were present. These are the only three cases I have seen at Bellevue Hospital.

GENERALIZED AMYLOIDOSIS. REPORT OF A CASE. DUNCAN MCCUAIG (by invitation)

The presenter described a case of advanced generalized amyloidosis discovered at autopsy in a woman, aged 64, from whose history as well as postmortem examination none of the usually ascribed, associated, chronic, cachectic states was discovered. Polycythemia was present. In a review of the literature, McCuaig discovered only one similar case. He attributed the polycythemia to stasis of the blood resulting from an extreme degree of amyloid deposition in the organs. The earlier and the more recent experimental work on the artificial production of amyloidosis in animals was described.

DISCUSSION

MILNDLL JACOBI. Some of the work of Jaffe in Chicago with the use of cholesterol and other lipoids in preventing the formation of amyloid was mentioned. In this connection I should like to call attention to the marked differences between Jaffe's results and those of Smetana and Kuczynski in obtaining amyloid in nonprotected animals, the latter regularly obtained amyloid after from seventeen to thirty injections of nutrose (sodium caseinate), whereas the former required from forty to sixty injections and delayed its formation only up to seventy injections.

I should also like to call attention to a paper presented at the Academy before the Society for Experimental Biology and Medicine by Dr. Grayzell and myself dealing with this problem. We produced amyloidosis in white mice kept on an ordinary laboratory diet, or one to which meat had been added, after from seventeen to twenty-six injections of nutrose, whereas only a few changes dimly suggestive of amyloid were produced after fifty-five injections into mice kept on a diet to which liver extract had been added, and definite changes were not apparent until the sixty-eighth injection. Even in these animals the amyloid was present in far lesser quantities and in more fragmentary arrangement. With Smetana, we found the earliest amyloid in the cells of the reticulo-endothelial system, rather than as an extracellular deposition.

PATHOGENESIS OF HYPERNEPHROMA. DAVID PERLA and J. GORTESMAN

An analysis of forty-four instances of hypernephroma from a clinical and pathologic point of view was made. Of these, sixteen instances were accidental observations seen at autopsy.

All gradations from benign structures to malignant hypernephroma were found in the same tumor.

All types of histologic variations may occur in the same tumor, such as cortical adenoma, typical hypernephroma, papillary and adenomatous forms and highly malignant carcinomatous and sarcoma-like infiltrations.

Comparative studies emphasize the histogenetic development of hypernephroma from cortical aberrant tissue. Cortical suprarenal rests in the kidney may grow into benign adenomas. At any period during the life of the individual such benign structures may become malignant. This development and subsequent metastatic dissemination proceed at a variable rate.

The neoplasm may exist for many years prior to the onset of symptoms.

There is extreme variation in the interval between the onset of symptoms and the death of the patient from the neoplasm.

In about half the cases the primary symptoms of neoplasm were referable to metastatic lesions such as the pelvis, skull, long bones, vagina and lungs.

Primary malignant neoplasm of the kidney with metastatic foci may exist for some time prior to the development of any symptoms.

DISCUSSION

M. A. GOLDZIEHER. This presentation of the subject has drawn attention to the appearance of pleomorphic tumor cells in the Grawitz tumors, as well as in the suprarenal cortical tumors. Nevertheless, the arguments and the pictures presented beautiful as they are do not convince me that the morphologic evidence presented by Stoerk and some of his followers may be disregarded. It would take too much time to go into the morphologic discrepancies between the opinion of Stoerk and that which we have heard. I want to draw attention to some of the biologic aspects of the question, which to my mind have at least as much weight as the morphologic considerations. One of these is a point that Lubarsch himself has raised, when he admitted that it was peculiar that the Grawitz tumors are rich in glycogen, whereas the cortical suprarenal tumors do not contain glycogen. Furthermore, I have seen cases of renal lipoidosis, particularly in infants suffering from some nutritional disturbance, in which the cells of the kidneys were so engorged with fat that they resembled most closely the cells presented, as typical suprarenal cortical cells. Finally, and this is the most important point, in all the cases of suprarenal cortical tumors that I have seen, and that is quite a number, and in all the cases reported in the literature, with few exceptions there is evidence of transformation of the sex character of that person, particularly if it is a woman. This action of the suprarenal cortical tumors is not present in Grawitz tumors of the kidneys. In none of them did I ever see any transformation of sex character, and to my knowledge there is no such observation recorded in the literature. However, tumors of the suprarenal cortex, both benign and malignant, are capable of transforming the sex character of the female in almost every case. Even the small adenomas frequently found in the cortex of old women are most probably responsible for the so-called old woman's beard, as I never fail to find them whenever I do an autopsy on an elderly woman with a hairy face. Yet tremendous tumors occurring in the kidney with or without metastases never produce such changes. I think that we are too much impressed by the morphologic similarity of the typical Grawitz tumor cells to suprarenal cortical cells, particularly in view of the fact that this similarity is restricted to the large foamy cells and does not hold as to the other cells of the small dense type, which are never absent in suprarenal cortical adenomas. Moreover, the polymorphism of the suprarenal cortical cells that has been emphasized here, and which I certainly admit, does not go so far as to produce real lumina with papillae. I also failed to see, in the demonstration here at least, what we would all admit to be papillary structures, therefore, I remain unconvinced of the suprarenal cortical origin of Grawitz' tumors, nor do I believe that they originate from suprarenal cortical cells, but rather from the renal epithelium. Finally, I want to mention that I have seen a few cases of renal cortical adenomas, in which I could follow a series of changes from the unquestionably renal adenoma type to a type somewhat similar to the so-called hypernephroma.

PAUL KLEMPERER. I think that it is hardly necessary for me to add to what Dr. Goldzieher said, but I should like to make my standpoint clear. I agree with Dr. Perla and Dr. Goldzieher that it is extremely difficult to settle the question as to the origin of the Grawitz tumor from the mere histologic evidence. I should like only to ask the question, On whom should actually fall the burden of proof that the Grawitz tumor originates from one of the tissues concerned? I do not think that it is correct to ask only the men who do not believe that the Grawitz tumor of the kidney originates exclusively from aberrant suprarenal tissue to prove that it originates from renal tissue. Actually, the proof should be shown by the men who believe that the Grawitz tumor originates from misplaced supra-

renal tissue. Is it not a rather peculiar fact that the overwhelming number of benign and malignant renal tumors should always originate from an aberrant tissue, and not from the homeotypical tissue? I think that this argument alone speaks in favor of the men who believe that the Grawitz tumor originates not from aberrant suprarenal tissue alone, but at times from the renal parenchyma.

From my studies of tumors of this type I have come to a conclusion opposite to that of Dr. Perla and Dr. Gottesman. They reached the conclusion that a tumor is of suprarenal origin in spite of the presence of glandular structures, for they have found areas in which the tumor apparently takes the structure of the fascicular zone of the suprarenal. I think just the opposite. In examining these tumors whenever I find an area in the section that apparently simulates suprarenal tissue, I look further. I am not satisfied to make the diagnosis of hypernephroma in a case in which I find evidence of glandular structures. I have never seen a benign or a malignant tumor of the suprarenal that had glandular structures, and I was not convinced from the pictures presented that the one tumor of the suprarenal presented showed actual glandular formation. One point that is always brought up in favor of the possibility that suprarenal tissue might become incorporated in the renal anlage is the close vicinity of both structures during embryonal life. I do not think that this is proof, or that there is any definite conclusion one might draw from this embryologic fact. Why do we not find just as frequently the same type of tumors in the testis or in the ovary, which after all in embryonal life are in close vicinity to the structure that later becomes the suprarenal gland? From the mere fact of the presence of large, clear cells, I do not think that one can make the diagnosis of hypernephroma, because they will be found in all possible locations. One tumor that was described years ago as a hypernephroma of the thyroid was most probably a parathyroid tumor. I have seen carcinomas of the breast which showed similar cells. It is well known that metastases often show structures very different from those of the primary tumor, and I think that we can often identify the true structure of the primary tumor from the metastases. To my mind, this experience explains the fact that Dr. Perla and Dr. Gottesman encountered tumors which in their primary location in the kidneys simulated suprarenal cortex, whereas the metastases exhibited glandular structures. I would not say that I consider it impossible to have a Grawitz tumor of suprarenal origin, but I doubt that it is frequently so.

ALFRED PRALT. I agree with the statements of Dr. Goldzieher, and as Dr. Klemperer just said, it is dangerous to make a definite diagnosis of a tumor because the tumor is mainly composed of large, clear cells. One of the arguments in favor of the hypernephric origin of Grawitz' tumors has been seen in the frequent location of Grawitz' tumors in the same regions in which aberrant suprarenal tissue is found. The ovary and the broad ligament belong to these regions, however, while aberrant suprarenal tissue is much more frequent in the ligament, the tumors in question occur much more frequently in the ovary. I had the opportunity of examining a large, solid, yellow, ovarian tumor that had been diagnosed by several physicians as a hypernephroma of the ovary. Examination of many blocks, however, finally led to a small part of the tumor which was a distinct fibro-epithelioma with small, narrow cells containing dark, small nuclei. While it is easy to understand how such small cells may become large, clear cells such as are found in the Grawitz tumor, by storing any soluble substances in the cytoplasm, I feel unable to see how such large, clear cells may be transformed into small ones. I may be permitted to take exception to the often repeated statement of the transformation of these large, clear cells into other epithelial cells with more compact cytoplasm. Thus, we cannot assume that the multiform picture of the tumors in question can be explained by secondary changes in cells that originally were large, clear cells. They probably came from cells that originally had quite a different aspect.

DAVID PERLA. In reply to Dr. Goldzieher, I do not want to go into this study in a controversial way, it is endless, and we could argue both ways just as readily.

One can see certain structures, and from them make certain deductions. I do not believe in laying too much stress on pure morphology. The two patients with tumors in the suprarenal glands showed no changes in the sex characters. There were no accompanying symptoms of virilism. Tumors in the suprarenal gland are frequently associated with virilism, but to say that a tumor arising in a cortical cyst is not a hypernephroma because it was not accompanied by physiologic changes carries no weight. We know that malignant tumors of the thyroid gland are not necessarily associated with hyperthyroidism. There can be extensive malignant tumors of the thyroid with widespread metastases and certainly no manifestations of functional change can be seen. As to aberrant tissue being found in other areas without tumors corresponding to hypernephroma, I can say only that if one denies that there is such a thing as hypernephroma, it is useless to argue about it. The three discussers have given me the impression that they believe that there is no such thing as a hypernephroma, but when we find tumors with large, foamy cells resembling aberrant cortical tissue, it is not without reason to assume that they might arise from such an aberrant tissue. Hypernephroma of the testis has been reported, and we know that the testis is the site of the aberrant tissue. It has been reported in the liver, where aberrant tissue has occasionally been found.

As to the variations in structure, I did not mean to imply that actually a large, foamy cell transformed itself into a small hyperchromatic cell, but that if you see a number of cells with all gradations of the quantity of lipid material in the cell and all gradations of the quantity of fluid in the cell, some being extremely hydropic, others having the characteristic fatty appearance with a kind of network, others showing less lipid and still others showing no lipid, staining homogeneously and definitely showing less cytoplasm, it is conceivable that all have had a common origin. The variation of the fluid in the cell, the variation of lipid and even the quantity of glycogen in a cell do not detract from the original source of that cell. I think that the presence of lipid and fluid in a cell depends on accidental physico-chemical conditions.

THE PATHOLOGIC AND PHYSIOLOGIC ASPECTS OF SIMPLE GOITER AS PRODUCED EXPERIMENTALLY IN RABBITS. BRUCE WEBSTER (by invitation)

For the past fifty years various attempts have been made to produce simple goiter experimentally with a view to discovering its etiologic factor. A few of these attempts have been partly successful. Notable among these are the goiters produced by Wegelin with cracker crumbs, by McCarrison with bacterial toxins and by Marine with liver and fats. In each of the foregoing instances, the amount of hyperplasia was not great, and the time required was long.

In the winter of 1927 thyroid enlargement was noticed among the rabbits that were being used for experimental syphilis at the Johns Hopkins Hospital, Baltimore. It soon became apparent that all animals maintained in the laboratory for more than four weeks showed an increase in the weight of the thyroid gland. This increase continued in direct proportion to the length of time that they were kept in the laboratory. These animals were being maintained under a standard laboratory regimen similar to that used in many other institutions. The diet consisted of 250 Gm of cabbage daily, and 50 Gm of oats and 20 Gm of hay once a week. All the animals were free from goiter on admission to the laboratory. Their nutrition was well maintained, the body fat being abundant. Except for an increase in the size of the thyroid gland, the animals were essentially normal at autopsy. There was a slight tendency toward an increase in the average heart/body-weight ratio.

Controlled experiments were carried out which established the fact that the cabbage in the diet was the causative factor in the production of goiter. Marine and his associates confirmed this observation and further demonstrated that all members of the *Brassica* group of vegetables were goitrogenous, while other closely related groups were relatively nongoitrogenous.

During the course of this work it became apparent that during the winter months (from October to March) goiter was more easily produced than during the

summer months. A reanalysis of the data showed that this had been the case since the work was begun at Baltimore in 1927. By a series of elimination experiments, it was possible to show that this seasonal variation is due to a seasonal change in the cabbage itself and not in environmental factors affecting the animal. Further, it was demonstrated that this seasonal variation occurs irrespective of any seasonal variation in the iodine content of the cabbage. The loose, rapidly maturing summer cabbage was found to be nongoitrogenous, irrespective of iodine content or source. The mature, slowly growing, so-called winter varieties manifest varying degrees of goiter-producing power. For the past two years, some change has occurred in late autumn which causes an abrupt increase in the goitrogenous power of cabbage grown under standard conditions. Attempts to correlate this with meteorologic changes so far have been unsuccessful. Cabbage of the slowly maturing variety imported from Holland has been found to be extremely goitrogenous. There was some evidence that there was a yearly as well as a seasonal variation in the goiter-producing power of cabbage.

In association with Dr. Marine, experiments were carried out to determine the nature of the substance in cabbage which produces goiter. The first question that arose was: Is the goitrogenous factor a positive one or a deficiency phenomenon? Repeated experiments showed that when an active goitrogenous cabbage was dried, either in air or in vacuo, it lost completely its goiter-producing power. Certain extractives had the same effect. These observations tend to suggest that a positive and not a deficiency factor is present.

Little has been found concerning the nature of this substance. Steaming the cabbage for thirty minutes tends to increase its goiter-producing power. If the steamed cabbage is pressed, the residue or cake contains all the goiter-producing material, while the juice contains none. The substance is not readily soluble in water, either at room temperature or at 100 C. Mild acid hydrolysis does not destroy this substance. Alkaline hydrolysis may destroy it to a slight extent.

Marine has expressed the idea that whatever the nature of this substance may be, it acts through the oxidation-reduction systems of the body, creating an increased demand for thyroxin and thus bringing about thyroid hyperplasia in an effort to meet this demand.

Pathologically, the goiter produced by cabbage is a simple hyperplasia of the thyroid gland, similar in type to all other simple goiters in man and animals. Glands weighing as much as 40 Gm. (approximately 400 times the normal size) have been encountered in rabbits. The vascularity of these glands was great. The enlargement was always diffuse. Gross nodules were not encountered.

Microscopically, the typical picture was that of struma diffusa parenchymatosa. Because of the small size of the follicle of a rabbit's thyroid gland, infoldings were rarely observed. The acinar epithelium was increased in height and the cells were predominantly of the chief type. The nuclei were large and vesicular. There was almost complete absence of colloid in all goiters of any appreciable size.

In rabbit goiters of less than a year's duration, adenomas were not observed. Marine expressed the opinion that adenomas rarely occur spontaneously in animals. The idea suggested itself, however, that it might be possible to produce so-called "involutionary adenomas" in rabbits by repeatedly causing the thyroid gland to become alternately hyperplastic and then involuted. Accordingly, three years ago, a number of young rabbits with large goiters were set aside for this purpose. Since that time they have alternated between periods of a cabbage diet and periods of iodization. In this way the attempt was made to reproduce the cycle of alternate hyperplasia and involution which takes place in an area of endemic goiter. These animals began to die of senility and the thyroid glands showed typical so-called "involutionary adenomas." The circulation was greatly distorted by areas of persistent hyperplasia and colloid cysts. There was an increase in stroma. In short, the condition resembled the early stages of a struma nodosa such as occurs in particular areas.

Goiters produced experimentally in this way were used as a source of material for various studies of simple goiter. The metabolism was studied in a series of

animals. It was found that those with large goiters had a metabolism approximately 166 per cent lower than that of normal animals of the same age. Later the development of goiter was observed in a group of animals, their metabolism fell from normal to a point almost at the level produced by total thyroidectomy. The animals showed changes in the skin and hair typical of mild myxedema. Once this low level of metabolism was reached, it remained constant for as long as a year, provided the patient was not treated for goiter.

The effect of the administration of iodine to these animals was then studied. Rabbits with large goiters were given intraperitoneal injections of 25 mg of potassium iodide daily. They lost weight rapidly, the thyroid glands decreased appreciably in size and the animals died in from two to seven days. Before death, their metabolism rose markedly, often to two or three times the normal level. At autopsy, the thyroid glands were in various stages of involution, depending on the period that had elapsed between the administration of iodine and death. By reducing the quantity of iodine administered, it was possible to cause an increase of metabolism which gradually subsided to a normal level. The administration of iodine to normal rabbits causes little or no change in the production of heat.

This increase of metabolism was regarded as a possible means of obtaining information about the quantitative relationship between available inorganic iodine and the hormone into which it is elaborated. On the basis of Marine's observation that 1 Gm of hyperplastic thyroid gland is capable of absorbing 1 mg of iodine, the metabolic changes produced by single minute quantities of iodine were studied. Briefly, these experiments suggested that in hyperplastic glands the quantity of thyroid hormone elaborated (as indicated by the changes in heat production) appeared to vary directly, within certain limits, with the amount of the available inorganic iodine.

By the injection of varying amounts of iodine, and by frequent biopsies from the glands, it was possible to study involution under controlled conditions. The degree of involution, as would be expected, depended on the amount of available iodine, together with the time that it was allowed to act. By varying these two factors, it was possible to obtain all stages from complete hyperplasia to a colloid goiter or complete involution, at different times in the same animal. The injection of as little as 1 mg of potassium iodide produces striking changes in the microscopic picture of these goiters. There is a rapid transition from the chief type of acinar cell to the colloid type. This suggests that these two types of cells, described by Langendorff, are in reality two phases of activity of the same cell.

An excess of iodine (75 mg per week) will completely prevent the development of goiter, irrespective of the potency of the cabbage fed.

In summary, the reactions given by this type of experimental goiter are essentially the same as those exhibited by simple goiter in man. Perhaps the only difference is the severity of the reaction observed when iodine is administered to animals with large goiters. This may be analogous to the increase in metabolism reported in various instances after the liberal use of iodine in areas of endemic goiter.

The foregoing material was presented largely as a method of producing goiter experimentally in a laboratory animal, under controlled conditions, with the hope that by means of this method some light may be thrown on the still unsettled question of the etiology of simple goiter.

LIPOID NEPHROSIS PAUL KLEMPERER AND (by invitation) A. B. KANTROWITZ

Two cases of pure lipoid nephrosis were presented. In one, that of a man, aged 48, repeated urinalyses gave negative results, during the course of anti-syphilitic treatment a generalized edema developed suddenly. Death occurred after the onset of erysipelas at the site of drainage by Southey tubes. In the other case, that of a boy, aged 2½ years, edema developed three months prior to his admission to the hospital. Death resulted from peritonitis, pneumococcus type IV being found in the blood stream and peritoneal fluid. Examination of the kidneys by the ordinary histologic methods—hematoxylin and eosin and

sudan stain—substantiated the clinical diagnosis of lipid nephrosis. The epithelium of the convoluted tubules in both cases was swollen, containing neutral and doubly refractile fat in the basal portions of the cells, while the hyaline droplets were found in the portions nearer the lumen. The glomeruli appeared normal.

A recent paper by E. T. Bell recommending the use of special staining methods necessitated a review of both of these cases. The application of the Heidenheim azo-carmin and the Lee-Brown modification of the Mallory aniline blue-orange G stains resulted in the recognition of finer histopathologic details, mainly within the glomeruli. A moderate degree of swelling of the glomerular endothelial cytoplasm and occasionally of its basement membrane was noted, especially in the second case. The swelling was caused by fine, neutral, fat droplets, also doubly refractile fats. In no case was there cellular exudation or glomerular epithelial or endothelial nuclear numerical increase. While the importance of the endothelial swelling cannot be minimized in glomerulonephritis, it must not assume an undue position in the absence of the other criteria of inflammation.

It was agreed with Bell that his recommended staining methods result in bringing out finer histologic details, however, the presenters disagreed with his conclusion that lipid nephrosis is a mild type of glomerulonephritis with only incomplete obstruction of the glomerular capillary loops, since in both cases presented the glomerular observations did not justify a diagnosis of inflammation.

This article will be published in full in *Deutsches Archiv für pathologische Anatomie und Physiologie und für klinische Medizin*.

DISCUSSION

IRVING GRAEF. I should like to ask Dr. Klemperer if he would carry his analogy between the storage of "fat" in the glomerular endothelium seen in his second case and the storage of "fat" seen in Niemann-Pick's disease to the point where he would postulate that such storage might lead to proliferation of the endothelial cells.

PAUL KLEMPERER. I think that regeneration following degeneration within the glomeruli, as in the tubular epithelium, may occur but even then the proliferation will be only a reparative phenomenon.

M. A. GOLDZIEHLER. The last words of Dr. Klemperer make it almost superfluous for me to say what I have in mind. I think that the whole point of Dr. Bell's criterion for the evidence of inflammation is the large number of nuclei. Whether in this case there are more nuclei than normally is a matter of opinion. I could not see more than in any ordinary glomeruli. However it is not fair to make a judgment on the evidence of photomicrographs, however excellent they be. If we see more nuclei it is important to distinguish what kind of nuclei they are. Dr. Bell mentioned that there were many hematogenous cells. I could not see them. The cells are either epithelial or endothelial. Let us take it for granted that in these cases of lipid nephrosis more endothelial cells are found. Any one who is familiar with the extensive deposit of lipid material in endothelial cells knows that, at a certain stage, these cells start to proliferate. After all, we know that proliferation is not the attribute of inflammatory lesions alone. Proliferation of endothelial cells is also an expression of a type of lesion of non-inflammatory origin. So in advanced lipid nephrosis there may be hyperplasia of the endothelial cells which to my mind would be no proof of the inflammatory nature of these lesions. In order to accept a lesion as inflammatory, I think that all pathologists, perhaps with the exception of Dr. Bell, admit that there must be more than hyperplasia of the endothelial cells. There must be cells of the leukocytic type, or, at least, if there are no leukocytes, there must be lymphocytes or some other hematogenic cells customarily seen in inflammatory conditions. Finally an inflammatory process is not complete from its morphologic aspect if we do not see cell damage and the storage of fat is not sufficient evidence of the impairment of a cell. Without these three basic criteria, the impaired cells, the exudation and the proliferation, I should not be prepared to accept the lesion as inflammatory.

Regular Meeting, Dec 17, 1930

LEILA CHARLTON KNOX, *President, in the Chair*

INJURIES OF THE PONS B M VANCE

The most common manifestation of injury to the pons is the presence of multiple small hemorrhages in its substance. In 328 cases of fracture of the skull, multiple pontile hemorrhages were demonstrated in 70 or 21.3 per cent. Similar lesions were found in 5 cases of injury of the head without fracture of the skull.

An analysis of these cases shows that the force that produced the injury was applied to the lateral portion of the head in 72 per cent, to the posterior portion in 24 per cent, to the frontal portion in 2 per cent and to the top of the head in 2 per cent. Apparently the mechanism that caused the pontile hemorrhages was not the same in every instance.

The anatomic relations of the pons to the basilar portion of the occipital bone, to the tentorium and to the other segments of the brain, suggest ways in which this portion of the brain stem can become traumatized. In many instances, violence applied to the cranium drives one of the cerebral hemispheres or the cerebellum on the pons and forces it against the basilar process. At other times, a lateral impact may cause the pons to injure itself against the sharp edge of the tentorium.

A case is shown in which the pons was practically severed by a lateral force which drove it against the edge of the tentorium. The deceased, a white man, aged 39, was struck by an automobile; he lived six hours. The skull was not fractured. There were lacerations of the temporal lobes and the cerebellum near the tentorium, and the pons was divided except for the subarachnoid membrane and the cerebral vessels.

Among seventy-five cases of spontaneous intracranial hemorrhage, multiple pontile hemorrhages were noted as accessory in ten. Four were cases of pachymeningitis interna hemorrhagica, four were cerebral hemorrhages in the basal nuclei, one was a subarachnoid hemorrhage in the fissure of Rolando and one was an aneurysm in the circle of Willis which had ruptured spontaneously. All these cases were associated with considerable unilateral intracranial pressure, and it is not unlikely that the tributaries of the veins of Galen which drain the pons were blocked, thus creating a condition that furthered the rupture of the blood vessels in its substance.

ALBERS-SCHOENBERG'S DISEASE "MARBLE BONES" M C PEASE (by invitation), A G DESAUNTS (by invitation), and NICHOLAS M AITER

In 1904, Albers-Schoenberg reported peculiar roentgen observations of the entire bony system. In these pictures the bony structures were replaced by a homogeneous "marble" appearance, hence the name "marble bones." Subsequent reports by Siek, Forey, Schulze, Lauterberg, Lievre, etc. emphasize the other cardinal symptoms of the disease entity. The disease can be traced back to childhood. The whole skeleton seems to be uniformly affected. After a lapse of time the bones become fragile. These fractures of the bone may not be associated with functional disturbances of other sorts (Albers-Schoenberg, Merrill, etc.). At a more advanced stage of the disease, atrophy of the optic nerve and severe anemia occur, which may lead to a fatal outcome. As there are only two cases reported in the American literature, with no pathologic information, the present case is reported with clinical, chemical and pathologic data. The German literature contains sixteen acceptable cases with a great variety of clinical and pathologic observations.

The patient, M. P., a girl, aged 8½ months, was admitted to the New York Post-Graduate Hospital with the complaints of blindness, "rolling of eyes" (nystagmus), pallor, enlargement of the abdomen and loss of weight. At the age of 2 months, the mother took the baby to a doctor for loss of weight and

"rolling of eyes" The doctor considered the symptoms due to feeding trouble, and the baby was treated accordingly. Finally, it was noticed that the child was apparently becoming blind. The weight remained practically stationary, and the abdomen was enlarging.

Physical examination on admission to the hospital showed a frail baby girl, underweight and irritable. The head was square, the anterior fontanel four fingerbreadths in the anteroposterior directions. Examination of the fundus of the eyes showed bilateral atrophy of the optic nerves. The nose was saddle-shaped. The lower incisor teeth were erupted. There was generalized enlargement of the lymph nodes. In the distended abdomen, the liver and spleen were palpable. There had been nothing to call attention to the bones. In the hospital, the patient's weight remained practically stationary (10 pounds, 11 ounces [4.8 Kg]). The temperature was normal, except for the last five days of life, when a terminal bronchopneumonia developed.

The conspicuous features of the laboratory examination were the anemia with leukocytosis and the calcium and phosphorus metabolic changes. There was a severe anemia of the hypochromic type, the changes of the red blood cells being as marked as in pernicious anemia. The white blood cells were considerably increased at times, and contained about 45 per cent myelocytes. Although the chemical examination of the blood showed nothing very striking, the amount of calcium was rather high and the phosphates rather low.

Röntgenologic examination showed fibrosclerotic thickening of all the long bones with pronounced thickening of the cortex and encroachment of the lumina of the long bones, which were of hour-glass shape. There was an old fracture near the junction of the middle and lower third of the left femur. At many places the structure of the bones was lost and had a white, "marble-like" appearance. Similar sclerosis was found at the base of the skull.

Symptoms of pulmonary involvement developed, the temperature rose and the patient died with symptoms of bilateral bronchopneumonia.

Abstract of Autopsy Protocol—The body was that of a poorly nourished female infant of 8½ months. The skin was pale. The anterior fontanel was four fingerbreadths in the sagittal direction. The costochondral junctions were swollen, resembling the rosary in rickets. The skull was sawn through with greater difficulty than in an adult on account of the extraordinary increase of resistance. The bones of the skull showed marked thickening and obliteration of the diploe. The bones of the base of the skull were also much thickened with narrowing of the foramina. The optic canal was markedly narrowed, compressing the optic nerve. The thymus, pituitary and thyroid glands were small. All the bones of the skeletal system showed marked changes. The cortex of all the long bones was markedly thickened, the outer periosteal surface was uneven and inwardly there was transition to less dense compact bone that was replacing the bone marrow cavity. The line of ossification was irregular. In size, the epiphysis was in proportion to the enlarged end of the diaphysis. On cross-section of the epiphysis, irregular gray calcified areas were seen scattered in the blue cartilage. Subperiosteal hemorrhages were found practically over all the bones. Histologic changes were striking, as there was no resemblance to the normal bony structure. There was no definite canal system found with the characteristic concentric lamination, but an osteoid matrix that formed irregular trabeculae surrounding small cavities that were partly filled by fibrous stroma with some fibroblasts. These, however, did not form a coherent surface layer of osteoblasts. There were numerous giant cells that were not unlike osteoclasts. Cellular infiltration was present, most of the cells being of the lymphocytic type with a small dark nucleus and practically no cytoplasm. There were no granular cells.

Familial character is suggested by the cases of Lorey, Reve and Sick. The majority of the cases have been found in the earliest childhood, from a few days after birth to 5 years. In the rest of the cases an early onset of the disease is suggested with a more benign prolonged course.

The changes of the bone of the entire skeleton, although they may be of different stages, are typical, and do not suggest relationship to other diseases of the

bone The lack of structure in x-ray pictures with the increased deposits of calcium is characteristic, and probably is the cause of the lack of elasticity and thus of the fragility of the bones The fractures may be quite frequent and heal apparently rapidly with exuberant callus This is also evidence of increased calcium content of the blood Histologically, the most conspicuous features are the lack of osteoblasts, the imperfect osteogenesis with lack of lamellation and excessive calcification of osteoid tissue There is a lack of bone marrow cavity and bone marrow formation Many of the clinical symptoms are easily understood from these pathologic changes The progressive anemia may lead to a fatal outcome without intervening infections This anemia is obviously due to the lack of activity of the bone marrow, that leads to extramedullary hematopoiesis It has even been suggested (Laurell-Wallgren, Lorey, etc) that the enlargement of the liver, spleen and lymph nodes has the same significance as a form of compensatory hyperplasia The increase of myelocytic cells in the blood with these organic changes resembles a leukemic condition Such cases with generalized osteosclerosis were reported by Jaksch, Nauwerck, etc, but Jores emphasizes the difference of this type of metaplastic bone formation in the marrow from the histology of the changes of the "marble bones" The histology of these changes of the bone also excludes syphilitic and rachitic origin In this case reported the evidence seems to be in favor of congenital abnormality of osteogenesis of the entire bone-forming system

DISCUSSION

M C PEASL, by invitation I do not know that I can add anything to Dr Alter's presentation, except a few more clinical details At birth, the physician did not notice anything wrong with the baby, and at the end of three or four weeks he turned it over to one of our pediatricians as a feeding case, who cared for it for five or six months, at the end of which time it was noticed that the child was apparently blind It was then sent into our wards A roentgen examination was made because of the deformity of the thigh Up to that time there was no suspicion that there was anything wrong with the bones, and the roentgen report showed this surprising condition The roentgenogram of the skull was one of the most characteristic plates, showing remarkable thickening at the base of the skull This child must have had a more acute case than some of those described in the literature, because the condition in the bones was not compatible with life To be sure she did die of bronchiopneumonia, but if she had not done so, death would have occurred from inanition, and that within a few weeks

There is another interesting thing in connection with this case Dr LeWald made a roentgen examination of the oldest brother of this baby for a condition supposed to be Hirschsprung's disease, but which was a dilatation of the sigmoid In this case the bones, so far as they were included in the plates, were normal That is interesting from the standpoint that as far as this particular case is concerned, we were not able to find any familial factor, and on further inquiry into the family history, I could find no evidence of a similar condition At the same time, cases have been reported in which there has been unmistakable evidence of a hereditary factor

There was little external change in the child When I came to the autopsy room the abdomen was being sewn up The pathologist reported that there was nothing interesting in the case, so I got the x-ray pictures, and we proceeded to do the autopsy over, and to remove some of the bones It is not, so far as we know, a common disease Perhaps if we watch for this condition, we may see it more frequently It is the only case of its kind I have ever seen, but perhaps we will see it more frequently if the attention of the medical profession is called to the possibility of such a disease

PAUL KLEMPERER One of the main questions for me in this interesting disease is whether Albers-Schoenberg's disease should be considered as an entity, as a disease *in genereis*, or whether it should not be thought of in connection with conditions that are possibly more familiar to us, and that become more

familiar every day, since the irradiation for leukemia has become a permanent therapeutic procedure. The first cases of osteosclerosis in leukemia were reported by Askanazy a few years before Albers-Schoenberg made his first report, and he considered the osteosclerosis in his cases as a kind of natural cure for the leukemia, by which he thought that the tissues producing blood cells, instead of producing blood cells had taken up the tendency to produce fibrous tissue. Similar cases have been reported by others and since x-rays and radium have been accepted in the treatment for leukemia, we not rarely encounter fibrosis of the bone marrow in examining the bones in chronic myeloid leukemia, which I think is related to the condition in Albers-Schoenberg's disease. Dr. Albers has emphasized that the absence of osteoblasts differentiates this condition from the osteosclerosis of leukemia. I feel, however, that it is possible that the osteoblasts are absent in a condition in which the bone formation is due to metaplasia of fibrous tissue, and in cases of leukemia treated with radiation I have seen that some of the extensive fibrous tissue, which is formed inside the bone marrow cavity and which actually more or less obliterates the bone marrow cavity, shows a tendency for deposits of calcium to become metaplastic bone. The question arises, In what way is it possible for the bone marrow to become a fibrous instead of a blood-forming tissue? I think it is not so difficult to explain if one considers the embryology of the bone marrow. In the first months when the primitive bone marrow cavity is formed from the periosteum, blood vessels grow into the cartilage, and they are accompanied by undifferentiated mesenchymal tissue, which begins to take up blood formation, and form the early hemoerythroblasts. The same tissue has the potentialities to form fibroblasts, and it depends on the stimulus which way it goes. Under roentgen treatment, apparently undifferentiated mesenchyme, which remains in the bone marrow to regenerate bone marrow during life, takes up the fibroblastic tendency and loses the hematopoietic tendency. The same occurs in these cases which have been described by Askanazy and others as osteosclerotic leukemias. In the case of Albers-Schoenberg's disease one can only think of a congenital perversion of the undifferentiated mesenchyme which instead of forming blood cells from the first, forms only fibroblasts. Such a congenital perversion would be one form of such an alteration of the differential potentialities of the mesenchyme, as it is expressed in the cases of leukemia under radiation treatment. It is not so surprising that the mesenchyme does not always fulfil the purpose it has under normal conditions. I remember one case of diffuse lipomatosis of the bone marrow in an adult, with severe chronic anemia. One can account for this condition in exactly the same way: the undifferentiated mesenchyme, instead of forming blood cells or fibroblasts takes up exclusively the storage of fats and in this way, instead of cellular bone marrow, only fat marrow is formed.

Should we not consider Albers-Schoenberg's disease a disease of the bone marrow rather than a disease of the bone? The predominance of the alteration of the blood picture in most cases possibly points in this direction. What were the changes in the spleen, the lymph nodes and the liver? Was there extensive blood formation? Was the picture one that reminded you of leukemia or was there merely an excessive compensatory extramedullary blood formation?

NICHOLAS ALILIK. I did not want to go into the explanation of what I meant by congenital absence of normal osteogenesis. I mean that there is an abnormal bone formation, and I think that is the only explanation: the perversion of the function of the bone marrow. I tried to emphasize it in the question of the histology, for I found nowhere a bony tissue of normal structure, and that feature differentiates it from the osteosclerosis, which one sees in leukemias or blood diseases of other types. There is an extensive literature on the leukemic changes of the bone in the German literature but they all show fibrosis of the bone marrow in conjunction with the normal osteogenesis, while here the osteogenesis is entirely absent. If it were due to that explanation we ought to see cases of Albers-Schoenberg's disease more frequently. That is also one of the arguments against syphilis.

I could find no evidence in the liver and spleen of hematopoietic function. When there is a leukemic picture where the nodes are enlarged, the enlargement of the spleen and lymph node take the place of the function of the bone, but in my case it did not.

AN EVALUATION OF THE ERYTHROCYTE SEDIMENTATION REACTION AS A ROUTINE DIAGNOSTIC PROCEDURE IN THE GENERAL HOSPITAL HELEN S. PITTMAN (by invitation)

The author gives a brief survey of the history of the sedimentation of erythrocytes. The method employed is the Westergren modification of the Fahraeus technique. The material presented includes results in 139 proved cases and 41 instances of arthritis from a series of 250 tests made on patients at St. Luke's Hospital in New York. Temperature, erythrocyte and leukocyte counts, and Wassermann reactions of the blood where available were recorded.

The series is divided into 23 controls, 41 cases of arthritis, 22 of malignant tumor, 17 of extra-abdominal infection and 75 from patients admitted complaining of abdominal pain. The latter group included salpingitis, appendicitis, fibromyomas of the uterus, carcinoma of the stomach and pancreas, peptic ulcer and cholecystitis and cholelithiasis. The effect on the rate of intake of the food and anemia are considered. In each instance recent literature is reviewed, and table and graphs of results are shown. From this series it is felt that the following points may be made. Blood counts in cases of anemia are distorted only with a red blood cell count of less than 3,000,000. Readings below 30 mm per hour are indicative of osteo-arthritis. Readings in excess of 40 mm per hour point to an infectious etiology. Between 20 and 40 mm per hour, both varieties are found. In malignant tumors the test was found to offer no diagnostic aid. The rate likewise is of no assistance in infections. In various abdominal conditions the rate is of assistance only when very much elevated above normal. Rates in excess of 80 mm per hour have been found only with acute suppurative processes in the lower part of the abdomen or pelvis. With rates below 50 mm, all conditions in the series were represented. The test is interpreted as being of diagnostic value only in the light of other clinical and laboratory observations.

DISCUSSION

ALFRED PIAUT: The influence of anemia on the sedimentation test has been mentioned. It is astonishing to see how divergent are the opinions expressed in the literature. From my own experience I agree with Dr. Pittman's statement that only a marked anemia interferes sufficiently with the sedimentation rate so that it must be considered clinically. A slight degree of anemia has no influence. I should like to know if Dr. Pittman thinks that the rapid rate in these higher grades of anemia is due to the relative increase in the plasma protein, or perhaps to the relative increase of cholesterol, which is not infrequent in some high grade anemias. I have no personal experience concerning this, but a comparison of the chemical analysis of the blood which may have been done for other reasons with the results of the sedimentation test might bring out some interesting facts.

As far as the much discussed question of the differentiation between acute salpingitis and acute appendicitis is concerned, I should like to know how much time elapsed between the onset of the first symptoms and the taking of the blood. The following reason is behind this question. When a woman becomes sick with an acute pain in the lower part of the abdomen, the disease does not start at that moment. The infection has been there for some time. That means there has been sufficient time for absorption from the infectious area, which as we assume leads to the increase in the sedimentation rate. On the other hand, when a person has pain in the right lower quadrant due to appendicitis, then we know that the infectious focus may be extremely small, and we assume that the inflammatory process is an early one, perhaps only a few hours or perhaps only one hour old. That could explain easily the fact that when one sees such a patient directly after

the onset of the abdominal pain, the sedimentation rate may be nearly normal. Therefore, in comparing the sedimentation rate in patients with appendicitis and acute salpingitis, I think one must know how much time has elapsed after the first attack of pain. I know that some people, when they see a normal sedimentation rate in spite of severe abdominal symptoms, exclude acute salpingitis, and then the remaining diagnostic points generally lead to the diagnosis of acute appendicitis. I should like to know where the surgeons of St. Luke's put the limit of operability. When everything else is normal but the sedimentation rate is high, some surgeons say "I do not operate unless it is below that point." I recall a patient who died after a seemingly safe operation, when nothing indicated any particular danger, and my opinion was asked if the sedimentation rate would have given a contraindication to operation. The chart really showed a high sedimentation rate.

As far as tumors are concerned, I wonder if one can expect a small scirrhous carcinoma to have the same effect on the sedimentation rate as, for instance, a large, ulcerating carcinoma of the intestine. I do not feel that carcinoma can be considered as an entity in its action on the sedimentation of the red blood cells.

HELEN P. PITTMAN. I am afraid I cannot tell you to what the increase in the sedimentation rate is due. I have contributed nothing to the theory of the phenomenon.

The two cases of acute appendicitis in which I found a very high rate were both in young people, one presenting symptoms for about forty hours, and the other between twenty-four and thirty-six hours.

Book Reviews

UEBER DIE AKUTE UND CHRONISCHE GELBE LEBERATROPHIE MIT BESONDERER BERUICKSICHTIGUNG IHRES EPIDEMISCHEN AUFTRETENS IN SCHWEDEN IM JAHERE 1927 By PROF DR HILDING BERGSTRAND, Stockholm Price, 14 Marks Pp 114, with 68 illustrations and 2 colored plates Leipzig Georg Thieme, 1930

The studies reported in this monograph are based primarily on the epidemic of acute yellow atrophy of the liver which occurred in Sweden in 1927. The 97 cases recorded in that year form the basis for the percentages quoted, but all available material from a total of 150 cases was used for study. In this epidemic, the disease was five times as prevalent in the cities as in the country, although only about one third of the population of Sweden is urban, it involved women in 72 per cent of the cases, it was most frequent between the ages of 30 and 60 years, and it was evident in two waves, one reaching a peak in July, the other a lower peak in November. Pregnancy and syphilis were negligible factors, because none of the women was pregnant or had been recently delivered, and only 1 patient was syphilitic.

To substantiate his contention that acute yellow atrophy is the result of infection, the author recorded all details relative to the clinical aspects of the disease. Symptoms in the upper respiratory tract and the gastro-intestinal tract most frequently preceded the atrophy of the liver, and 16 per cent of the patients were operated on because the symptoms simulated gallstone colic. After this prodromal stage, 76 per cent of the patients became jaundiced. The anatomic picture was a central necrosis in the liver lobules of greater or less extent, followed by regeneration and replacement of scar tissue. The center of the lobule is the seat of greatest damage, presumably because it contains the greatest amount of venous blood. Studies of corrosive preparations seem to indicate that whole regions in the liver are normally more venous than others, and thus more extensive damage to the liver is evident in such places, as in the front surface near the suspensory ligament. Four gross liver types are recorded, a coarsely nodular type, resembling a *hepar lobatum*, a Laennec type, a coarsely granular type and a finely granular type. The latter two are associated with the more chronic cases.

CLINICAL ALLERGY, PARTICULARLY ASTHMA AND HAY FEVER, MECHANISM AND TREATMENT By FRANCIS M RACKEMANN, M.D., Physician to the Massachusetts General Hospital, Instructor in Medicine, Harvard Medical School, Boston Price, \$10.50 Pp 617, with 30 figures New York The Macmillan Company, 1931

The main object of this book is "to define the present-day conception of the mechanism of asthma, hay-fever and allied disorders and then to discuss the methods of diagnosis and treatment with the results obtained." Part I, consisting of 220 pages, is devoted to a consideration of the phenomenon of hypersensitivity—history, experimental basis, chemistry, immunology, desensitization, bacterial allergy, and nature, origin and diagnosis. Perhaps the discussion in this part may be more technical, more detailed and more elaborate than is really necessary, but the author makes an earnest attempt to establish the distinctions between allergy, immunity and "normality." One of the difficulties lies in the circumstance that certain terms, e.g., allergy, have been given different meanings at different times. Many of the questions that present themselves in this field cannot now be answered satisfactorily. Part II, of about 355 pages, deals with the clinical manifestations of allergy—serum disease, hay-fever, vasomotor rhinitis, asthma

(seven chapters), urticaria, erythema multiforme, angioneurotic edema, eczema, migraine and other manifestations of hypersensitiveness. At the end of each chapter is a list of pertinent references. The last chapter presents an interesting, comprehensive discussion and summary. In the appendix is a useful list of allergens, except pollens, and also a list of patent medicines used in the treatment for asthma and hay-fever. There are thirty black and white illustrations, mostly of practical clinical interest. The book is printed in clear type on glazed paper that seems thicker and heavier than necessary. There can be no question of the value of the book, especially its second part, to the clinician, whether he is engaged in private practice or in special clinical work. The monograph presents the results of a rich experience in the application of immunologic principles to the diagnosis, prevention and treatment of so-called allergic diseases, and on that account it will also have a special interest for the immunologist.

INTESTINAL TUBERCULOSIS, ITS IMPORTANCE, DIAGNOSIS AND TREATMENT. A STUDY OF THE SECONDARY ULCERATIVE TYPE. By LAWRENCE BROWN, M.D., Consultant to the Trudeau Sanatorium, Saranac Lake, New York, and HOMER L. SAMPSON, Roentgenographer of the Trudeau Sanatorium, Saranac Lake, New York. Second edition, thoroughly revised. Cloth. Price, \$4.75. Pp. 376, with 122 engravings and 2 colored plates. Philadelphia: Lea & Febiger, 1930.

The fact that a second edition of this monograph—although dealing with a rather specialized topic—is published four years after the first attests to the vital interest which it evoked. In the meantime a great deal of discussion has gone on about the theses of the authors, to wit: that ulcerative tuberculosis of the intestines is not necessarily a late complication of pulmonary tuberculosis, that its diagnosis can be made roentgenologically, and that in a high percentage of cases ultraviolet irradiation affords symptomatic relief and produces healing in some. The numerous publications on these questions that have been published since 1926 have swelled the biography of the book from twenty-one to twenty-seven pages. But the dissenting opinions on the reliability of the diagnostic procedures are rather summarily disposed of in the foreword and are explained mainly by faulty technique. It might, however, be mentioned that the clinical material at the disposal of the authors is not particularly suited to establish the specificity of their method. The main additions to the book are an elaboration on the technique of the roentgenologic diagnosis, and a welcome enlargement of the chapter on "Pathological Anatomy of Intestinal Tuberculosis," which appears now under the name of its author, L. U. Gardner. This chapter, which is based entirely on the thorough work of its author on a rich and well analyzed material, deserves particular praise. The monograph covers, in addition to the specific subject, competent and clear discussions on the anatomy and physiology of the intestines. It is again warmly recommended to the attention of all those in medical work who are interested in intestinal tuberculosis.

TECHNIQUES HISTOLOGIQUES DE NEUROPATHOLOGIE. By IVAN BERTRAND, Directeur à l'Ecole pratique des hautes études, Chef de laboratoire de la Clinique neurologique de la Salpêtrière. Preface du Professeur G. Guillain. Price, 50 francs. Pp. 376. Paris: Masson & Cie, 1930.

As Guillain justly remarks in the introduction to Bertrand's book, the progress of modern neurology can be advanced best by the combined knowledge of both clinical and pathologic fields. The success of the pathologic phase depends much on the staining methods. Unfortunately, during the last twenty-five years the latter became so numerous that it is not possible even for a specialist to master them all, while an average laboratory worker is unable to orient himself as to their relative merits. Too often they are not accessible because they are scattered in the numerous journals, many in foreign countries. For this reason Bertrand's manual is invaluable, and as he is an experienced and indefatigable worker in

the fields of pathology and neuropathology, he is competent to guide one through the mass of methods and to emphasize those that are the most important and valuable. Concise as he is in his description and much as he has reduced the number of the methods, it required a respectable volume to present the subject satisfactorily. Short chapters deal also with the gross methods of examination of the central nervous system, from the time of the delivery of the cadaver to the necropsy room to that of the sectioning of the brain and its staining. A concise outline is given of the methods of examination of the peripheral nerves and of the use of the infra-red light in cytologic studies and photomicrography of the central nervous system. Bacteriologic features pertaining to the central nervous system, mitochondria and connective tissue are fully discussed in separate chapters. On the whole, it is an excellent and indispensable manual written in clear and plain language and excellently edited.

TUBERCULOSIS IN MAN AND LOWER ANIMALS. By H. H. SCOTT. Special Report Series, No 149, Medical Research Council. Price, 4 Shillings. Pp 270. London. His Majesty's Stationery Office, 1930.

In this book are assembled a set of useful records in the comparative pathologic anatomy of spontaneous tuberculosis in man, wild animals in captivity, birds and reptiles. A considerable portion of the book is devoted to tabular summaries of necropsies of tuberculous human patients and animals, with discussion directed toward the varying character and distribution of lesions in the different species. The material is drawn from postmortem records of Chinese of the laboring class in Hong Kong, and wild animals dying of tuberculosis in captivity in the Zoological Gardens of London. The book will prove valuable to all who have occasion to consider the manifestations of tuberculosis in animals of varying habits of life and of varying susceptibility to the disease.

Books Received

THE PATHOLOGY OF INTERNAL DISEASES By William Boyd, M.D., M.R.C.P. (Ed.), Dipl. Psych., F.R.S.C., Professor of Pathology, University of Manitoba, Pathologist to the Winnipeg General Hospital, Winnipeg, Canada Price, cloth, \$10, net Pp 888, with 298 illustrations Philadelphia Lea & Febiger, 1931

THE FACTOR OF INFECTION IN THE RHEUMATIC STATE By Alvin F. Coburn, Resident Physician Presbyterian Hospital in the City of New York Price, \$6.00 Pp 288, with 48 illustrations Baltimore Williams & Wilkins Company, 1930

PROBLEMS AND METHODS OF RESEARCH IN PROTOZOOLOGY By Twenty-Seven Contributors Edited by Robert Hegner, Professor of Protozoology, and Justin Andrews, Associate in Protozoology, Johns Hopkins University School of Hygiene and Public Health Price, cloth, \$5 Pp 532, with 32 illustrations New York The Macmillan Company, 1930

PATHOLOGISCHE ANATOMIE UND HISTOLOGIE DER VIRKUNGEN Bearbeitet von Dr. Else Petri, Berlin Bildet Band X vom Handbuch der speziellen pathologischen Anatomie und Histologie herausgegeben von F. Henke und O. Lubarsch Price, 144 marks, bound, 148 marks Pp 724, with 96 illustrations Berlin Julius Springer, 1930

VERHANDLUNGEN DER DEUTSCHEN PATHOLOGISCHEN GESELLSCHAFT Im Auftrage des Vorstandes herausgegeben von dem derzeitigen Schriftführer G. Schmoll in Dresden Fünfundzwanzigste Tagung gehalten in Berlin am 3-5 April, 1930 Generalregister zu Tagung 21-25 Mit 114 Abbildungen im Text und 9 Tafeln Pp 422 Jena Gustav Fischer, 1930

ANATOMIE UND PATHOLOGIE DER SPONTANERKRANKUNGEN DER KLEINEN LABORATORIUMSTIERE: KANINCHEN, MEERSCHEINCHEN, RATTE, MAUS Herausgegeben von Rudolf Jaffe, Berlin Mit 270 zum Teil farbigen Abbildungen Price, 98 marks, bound, 102 marks Pp 832 Berlin Julius Springer, 1931

A STUDY IN NUTRITION AN INQUIRY INTO THE DIET OF 154 FAMILIES OF ST. ANDREWS By E. P. Cathcart and A. M. T. Murray, assisted by M. Shanks Medical Research Council Special Report Series, no 151 Price, 1 shilling, net Pp 60 London His Majesty's Stationery Office, 1931

HANDBOOK OF PROTOZOOLOGY By Richard R. Kudo, D.Sc., Assistant Professor of Zoology, University of Illinois Price, \$5.50, postpaid Pp 451, with 175 etchings containing 1,463 figures Springfield Charles C. Thomas, 1931

THE CLINICAL INTERPRETATION OF BLOOD EXAMINATIONS By Robert A. Kilduffe, M.D., Director, Laboratories, Atlantic City Hospital Price, cloth, \$6.50, net Pp 629, with illustrations Philadelphia Lea & Febiger, 1931

THE NINTH SCIENTIFIC REPORT ON THE INVESTIGATIONS OF THE IMPERIAL CANCER RESEARCH FUND Under the Direction of the Royal College of Physicians of London and the Royal College of Surgeons of England Price, 20 shillings Pp 156 London Taylor and Francis, 1930

EMBOLISM AND THROMBOSIS

PROLONGED DIRECT OBSERVATION OF THE PHENOMENA IN PIAL
VESSELS OF THE LIVING CAT *

AUBREY WEBSTER ARMENTROUT, M D
UNIVERSITY, VA

The present status of knowledge concerning embolism and thrombosis has been attained through clinical examinations, autopsies, experiments on animals and observations made directly on the streaming blood. The original object in this investigation was the study, by direct observation in the living animal, of the effects produced by fat emboli in the pial blood vessels and the comparison of these effects with those produced by various other foreign body emboli. The results are perhaps more significant from the point of view of the fundamental problems of embolism and thrombosis.

Welch¹ defined embolism as the "impaction in some part of the vascular system of any undissolved material brought there by the blood current." He stated further that "an embolus is the starting-point of a secondary thrombus which usually, although not always, completes the closure of the vessel, if this was not effected by the embolus itself, and extends on each side to the nearest branch," and that "whereas the introduction of such foreign bodies as threads, or bristles with rough surface, into the circulation is an efficient cause for thrombosis, perfectly smooth indifferent bodies as small glass balls, may be introduced without causing coagulation."

Zahn,² in 1872, was one of the first to make a systematic study of the formation of thrombi. He distinguished the red, or "coagulating," thrombi from the white, or "separating," thrombi, and by direct observations on the circulating blood in the mesenteric blood vessels of the frog, he was able to follow the inception of the latter. He observed, that, following a sticking injury of the wall of the blood vessel, a white

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¹ This work was done during a year's tenure of a Philip Francis du Pont research fellowship

¹ Welch, W. H. Thrombosis, in Papers and Addresses, Baltimore, Johns Hopkins Press, 1920, vol 1, p 110, Embolism, *ibid*, p 193

² Zahn, W. Untersuchung über Thrombose Bildung der Thromben, Virchows Arch f path Anat 62 81, 1875

thrombus began to form, the process being initiated by collections of white blood cells at the point of injury. These, he later noticed, broke down into a finely granular mass. In this same series of experiments threads were introduced into veins, and it was noticed that thrombosis sufficient to close the vessel occurred only in a very weak stream. In a stream of normal speed only a thin layer of cells occurred about the thread. From these experiments he concluded that the red thrombi are caused by a coagulation of the blood, while the white thrombus is a product of a "separation" of the blood, the latter being started by the accumulation of white blood cells.

Following the description of the blood platelets by Hayem, these began to be considered as important components in the formation of the white thrombi. In 1882, Bizzozero,⁴ repeated the observations made by Zahn, using however, the mesenteric blood vessels of the cat instead of those of the frog. The mesentery was floated out over the stage of the microscope in salt solution, and observations were made by means of a water immersion lens. With this apparatus, by observing a small blood vessel, he could see a third formed element circulating between the other elements of the blood. This he identified as the blood platelet, already described. On pressing the vessel that was under observation with a sharp needle he noticed a collection of platelets at the point of injury. At first only a few were deposited, but in a short time there were large accumulations. A few blood cells also became attached. As the thrombus grew, it filled the lumen of the vessel and hindered more and more the flow of blood. However, if the stream was strong, the entire thrombus, or only a part of it, was carried away, forming a platelet embolus. This process he observed many times in the same vessel, as often perhaps as three or four times in the course of fifteen minutes, and it was repeated for hours until the experiment ended. It was also noticed that simple jarring of the vessel by accidentally hitting the microscope might produce a similar formation, but to a less extent.

To observe the formation of thrombi on foreign bodies, Bizzozero introduced strings into the jugular veins of dogs and rabbits. When the string was left in the vein for fifteen minutes, there was found about it a small white thrombus, composed chiefly of platelets, but with a few white blood cells present in the periphery. If the string was left for an hour, the platelets in the center were found to have formed into a finely

3 Hayem, G. *L'anatomie normal et pathologique du sang*, Paris, 1878.

4 Bizzozero J. *Ueber einen neuen Formbestandtheil des Blutes und dessen Rolle bei Thrombose und der Blutgerinnung*, Virchows Arch. f. path. Anat. **90** 261, 1882.

granular mass From these experiments Bizzozero concluded that the blood platelets, and not the white blood cells, play the most important part in the formation of white thrombi, and that the granular substance, formerly ascribed to a decomposition of white blood cells, results from an alteration of the platelets

In 1886, Eberth and Schimmelbusch,⁵ also working with mammals, confirmed the work of Bizzozero as to the initiation of the white thrombus by the accumulation of platelets They, however, considered that this process is dominated by the mechanical relations of the blood stream By observing the normal stream they found that all the blood platelets and all the red blood cells, because of their greater specific gravity and the unequal velocity in the individual portions of the lumen, flow in the middle of the vessel surrounded by an envelope of plasma, in which only a few of the relatively light leukocytes are found If the velocity of the blood stream is decreased, more white blood cells and then the platelets are distributed in the plasma zone Because of this characteristic they argued that no thrombosis can take place in a normally flowing stream, even if the wall of the vessel is injured, as no platelets can come in contact with the endothelial defect When, however, there is a slowing of the stream with a change in the vascular wall, there results at the place where the vascular wall is not intact, an accumulation of blood platelets This accumulation is considered to be a result of a "viscous metamorphosis" in the platelets From their observations they concluded first, that mechanical changes in the blood stream are as essential for thrombosis as is injury to the wall of the blood vessel, and second, that the white thrombus is formed from preformed blood constituents and results from an accumulation of blood platelets, wherein a few red and white corpuscles are accidentally included Therefore, they considered the formation of a thrombus a result of a "conglutination" and not of a "coagulation"

Welch,⁶ in 1887, using ligatures, foreign bodies and caustics, confirmed in many respects the work of Eberth and Schimmelbusch, but disagreed about the part played by coagulation In the thrombi produced he was able to demonstrate the presence of fibrin as early as five minutes after the application of the ligatures, in some instances, and after fifteen minutes very often A considerable amount of fibrin was found uniformly at the end of half an hour On the basis of these results

5 Eberth, J. C., and Schimmelbusch, C. *Experimentelle Untersuchungen über Thrombose*, Virchows Arch f path Anat **53** 39, 1886

6 Welch, W. H. *The Structure of White Thrombi*, in *Papers and Addresses*, Baltimore, Johns Hopkins Press, 1920, vol 1, p 47

the attempt to draw a sharp distinction between thrombi formed by conglutination and those formed by coagulation was considered unwarranted. Welch also showed that thrombosis often fails to be produced following the action of caustics, scraping the interior of the blood vessel and so forth when the stream is not slowed.

Beneke,⁷ in 1913 directly observing the streaming blood, emphasized again the mechanical changes in the stream. He observed that when a partial obstruction is produced in the blood stream, there is developed peripherally to the obstruction a small eddy or whirlpool. Into this eddy platelets are collected and held, later becoming attached to the point of injury or being carried away in the blood stream. The same phenomenon was noticed where there was a sudden widening of the blood stream.

The part played by bacteria in the formation of thrombi about foreign bodies in the blood stream was demonstrated by McLean.⁸ In 1915, he found that when a sterile thread is introduced into the lumen of a vein so that about from one half to three fourths of an inch (1.27 to 1.88 cm.) remains suspended in the vein oscillating in the blood stream no thrombus forms on the thread or at the point of introduction of the thread. The same was found to hold true in the case of an artery even if the thread remained in the vessel for from four to seven days. If, however, a thread that had been contaminated with a culture of *Staphylococcus albus* or *aureus* was introduced there was found a large thrombus at the end of four days when a vein was used, and at the end of five days when an artery was used. From this it was concluded that infection and necrosis, or the toxins derived from an infectious and necrotic process, are probably the most important factors in the production of a thrombus.

Shionoya,⁹ in 1927, studied the formation of thrombi in an extra-corporeal loop. By shunting the blood from the carotid artery into the jugular vein through a collodion tube he was able to watch the formation of thrombi in its passage over this foreign body. It was found that the circulation through the loop ceased in the normal animal in from six to ten minutes. The formation of white thrombi was noticed to start in from two to three minutes after the beginning of circulation through the loop and fibrin appeared two or three minutes later.

From the foregoing review one may conclude that thrombosis starts by an accumulation of platelets at the point of injury to the wall of the

7 Beneke, R. in Krehl-Marchand. Handbuch der allgemeinen Pathologie. Leipzig, S. Hirzel, 1913 vol 2 p 130, sec 2.

8 McLean, A. Thrombosis and Embolism, Surg. Gynec. Obst. **20** 457, 1915.

9 Shionoya, T. Thrombus Formation in Normal Blood in the Extravascular Loop, J. Exper. Med. **46** 13, 1927.

blood vessel. In a short time from two to three minutes, fibrin is present in the thrombus. The progress of this thrombus then depends on the strength of the circulating stream and on the presence of bacteria or of necrotic or injured tissue. From the experiments of Bizzozzerio it is evident that very young thrombi are weak, probably owing to a lack of any large amount of fibrin in the early stages, and that in a fairly brisk stream they may be repeatedly broken off and swept away. It should be noted that most of the experiments mentioned were carried out with an injured vascular wall at the site of, or in close proximity to, formation of the thrombus.

It may also be concluded that on the surface of rough foreign bodies thrombosis starts in the same way as at points of injury to the wall of the blood vessel, but that about smooth objects, such as glass balls, thrombosis does not occur.

Fat embolism was first observed in experimental animals by Magendie¹⁰ in 1821. In attempting to increase the viscosity of the blood, Magendie thought that the introduction of so innocent a substance as fat would cause no inconvenience. However, a few minutes after the injection of an ounce of oil into a vein of his experimental animal, the animal died. At autopsy he found that the circulation and respiration had failed because of the inability of the blood to return to the left side of the heart owing to the blocking of the pulmonary capillaries with oil.

Fat embolism has now become a subject of considerable importance, many clinical cases have been reported, and a large amount of experimental work has been done.

Zenker¹¹ and Wagner,¹² in 1862, reported the first cases of fat embolism occurring in man. The first of these was observed in a man who had received a crushing injury with multiple fractures of the ribs and lacerations of the liver and stomach. Warthin in 1913, in an extensive review of the literature, found the total number of cases to be about 350 though many of these he thought were not so clearly defined as to place them beyond doubt.

The occurrence of fat embolism following disturbances to depots of fat has been demonstrated in numerous reports of cases and experimental observations. Among these may be cited those of Warthin,¹³

10 Magendie, M. Note sur l'introduction des liquides visqueux dans les organes de la circulation et sur la formation du foie gras des vaisseaux. *J. de physiol. et de path. gen.*, 1821, p. 37.

11 Zenker, cited by Welch (footnote 1, second reference).

12 Wagner, cited by Welch (footnote 1, second reference).

13 Warthin, A. S. Traumatic Lipemia and Fatty Embolism. *Internat. Clin.* 4 (s. 23) 117, 1913.

Gauss,¹⁴ Weiman,¹⁵ Corlette,¹⁶ Bissell,¹⁷ Siegmund,¹⁸ Clarke,¹⁹ Sutton²⁰ and Caldwell and Huber²¹ That it may also occur without trauma has recently been emphasized by Lehman and Moore²² After a review of conditions under which this may occur they divided them into metabolic disturbances, poisonings, toxemias from acute infections and toxemias from the destruction of tissue They considered that in these cases the fat, circulating in the blood stream ordinarily in a very fine emulsion, is changed so that an agglomeration of these small particles takes place, and that in this way fat globules are built up to a size sufficient to plug capillaries Experimentally they were able to produce fat embolism in animals by intravenous injection of ether during the stage of digestive lipemia

Because of clinical manifestations fat embolism is usually spoken of as cerebral or pulmonary That a sharp distinction cannot be drawn between the two was demonstrated by Nakata,²³ Reuter²⁴ and others, who showed that fat is able to pass the pulmonary capillaries and those of the greater circulation The changes taking place in the brain following embolism have been described by Warthin, Weiman and Gauss Grossly the brain shows scattered small hemorrhages, to which the name "cerebral purpura" has sometimes been given These are usually extremely small and occur most often in the white matter, though at times they may be found in the gray Microscopically these hemorrhages are found to surround a small area of degenerating or necrotic cerebral tissue, in the center of which is a small blood vessel filled with fat Edema is frequently marked, and at times there is a slight infiltration by round cells, though this is never marked and

14 Gauss, H Studies in Cerebral Fat Embolism, *Arch Int Med* **18** 76, 1916

15 Weiman, W Ueber die Hirnveränderungen bei cerebraler Fettembolie, *Deutsche Ztschr f d ges gerichtl Med* **13** 95, 1929

16 Corlette, C E On Cerebral Fat Embolism Report of a Case with Recovery, *M J Australia* **1** 229, 1925

17 Bissell, W W Pulmonary Fat Embolism, *Surg Gynec Obst* **25** 8, 1917

18 Siegmund, H Fettembolie als Todesursache, *Deutsche mil-arztl Ztschr* **47** 407, 1918

19 Clarke, B E Fat Embolism Report of Two Fatal Cases Following Orthopedic Operations, *J A M A* **88** 919, 1927

20 Sutton, G E Pulmonary Fat Embolism, *Ann Surg* **76** 581, 1922

21 Caldwell, G T and Huber, H L Fat Embolism Following Trauma to Bones, *Surg Gynec Obst* **25** 650, 1927

22 Lehman, E P, and Moore, R M Fat Embolism, Including Experimental Production Without Trauma, *Arch Surg* **14** 621, 1927

23 Nakata, T Recherches sur la question de l'embolie graisseuse de la petite et de la grande circulations, *Rev med de la Suisse Rom* **38** 486, 1918

24 Reuter, W Experimentelle Untersuchungen über Fettembolie, *Frankfurt Ztschr f Path* **17** 205, 1915

is usually diffuse, not assuming the shape of a ring, as do the extravasated red blood cells. As to the time of appearance of the hemorrhages there are different opinions. Ribbert²⁵ said that they appear after the third day, Grondahl²⁶ found them after fifty hours, and Warthin reported finding them in a patient dying twelve hours after injury.

In the lung the successive changes taking place have been studied in a series of experimental animals by Lehman and McNattin²⁷. It was found that within a short time after intravenous injection of cottonseed oil there are milia hemorrhages and areas of edema in the lung. Following this, probably within a few hours, there is infiltration with polymorphonuclear and mononuclear leukocytes, and within a few days endothelial leukocytes and fibroblasts appear. The process may then progress to a scarring of the lung, with an increase of fibrous tissue, or, if an acute inflammation is superimposed, bronchopneumonia with purulent bronchitis may develop.

Paul and Windholz²⁸ emphasized the part played by fat emboli in the kidneys. They were able to collect a number of cases in which the patient's condition just before death resembled in many respects that of patients dying in uremia. They were able to show, by repeated intravenous injections of small amounts of fat in experimental animals, a marked rise in the retention of nitrogen. They considered, therefore, that the coma frequently noticed in these cases is due in part to the uremia produced and not entirely to the cerebral emboli.

In a rather extensive search through the literature only one report could be found of a case in which there had been direct observation of fat emboli in the streaming blood, this having been published by Jacobi and Magnus²⁹ in 1926. Through a trephined opening in the dog's skull, they were able to watch the effect of various kinds of emboli on the vasomotor activity of the cerebral vessels. For their observations no covering for the exposed pia was used. It was found that when the filtrate from a solution of amyl nitrite in from 5 to 8 per cent alcohol was injected into the carotid artery of the side which they were observing, blood clots could be seen in the blood vessels of the pia. There was noticed, in addition to the stasis produced by the

25 Ribbert, cited by Corlette (footnote 16)

26 Grondahl, cited by Corlette (footnote 16)

27 Lehman, E. P., and McNattin, R. F. Fat Embolism, Pathology of Lungs in Experimental Fat Embolism, *South M. J.* **22** 201, 1929

28 Paul, F., and Windholz, F. Experimentelle Studien über die Fettembolie und den durch sie verursachten Tod, *Mitt. d. Grenzgeb. d. Med. u. Chir.* **38** 614, 1925

29 Jacobi, W., and Magnus, G. Experimentelle Beiträge zur Frage der Hirn-embolie, *Deutsche Ztschr. f. Nervenhe.* **91** 219, 1926

fragmented column of blood a contraction of the vessel extending for some distance beyond the embolus. This picture did not last long, having cleared after the first injection within two minutes. After a second like injection the vessels had not returned to normal at the end of seven minutes. Injections of ink and air were found to produce a somewhat similar picture, the vascular contractions being always prominent. The circulation did not recover in cases in which air was used. When fat was injected, however, there followed no such contraction, and the column of blood came up into contact with the fat, pushing it on ahead, so that the circulation soon recovered to an approximately normal state.

From these experiments they concluded that following embolism from blood clot (produced by amyl nitrite in alcohol), ink and air, there is produced at the point of occlusion and beyond it a vascular contraction which causes circulatory disturbances exceeding those actually produced by the embolus. On the other hand, it was noticed that fat produces no such contraction. This is given as the explanation why fat emboli are frequently less injurious than other types of emboli.

It is to be emphasized that this study was made without protection of the blood vessels and under uncontrolled conditions of pressure. This may account for the differences in the observations made by these workers and the observations to be described here.

EXPERIMENTAL METHOD

The method employed in the present series of experiments is that of Forbes used by Cobb and Forbes in their studies of circulatory phenomena in the pia. For a detailed description the reader is referred to the article by Forbes,³⁰ in which the method is fully illustrated, a review of the various methods previously employed is also given.

A brief description of the apparatus³¹ will be given here for the convenience of those not already familiar with it. Of primary interest is the specially designed glass window, head clamp and mechanical stage for carrying the microscope.

The window is composed of a heavy metal ring, which is beveled and threaded so that it can be screwed into a trephined opening in the skull. In the bottom of this ring a circular cover glass is fastened. The metal ring is perforated by two holes, and into each of these the shaft of a 17 gage hypodermic needle is soldered. As these holes connect with the under surface of the window, fluid can be injected through the needle and air can be removed from beneath the window, when the latter is in place.

30 Forbes, H. S. The Cerebral Circulation. Observations and Measurement of the Pial Vessels, *Arch. Neurol. & Psychiat.* **19**: 751, 1928.

31 This apparatus was made in the laboratories of the Harvard Medical School under the direction of Dr. Forbes.

The clamp for holding the head is made of heavy steel. It has three screws with swivel points, which are placed in such a manner that when they are tightened on the skull of a cat, the head is held firmly in one position with the left parietal region well exposed (fig 1). The mechanical stage for carrying the microscope is made of heavy brass, and when fastened to the operating table it can be adjusted to any desired field by means of two screws. Because of the close proximity of the animal's head it is necessary to remove the ordinary stage and substage from the microscope before attempting to use it. For illumination a carbon arc has been used instead of the filament lamp originally described, this has been found satisfactory, though possibly not as steady as the other type of light. The beam is filtered through a 10 per cent aqueous solution of copper sulphate to which a few drops of saturated aqueous solution of picric acid have been added. This gives a green beam of light which throws the arteries and veins into deeper contrast and gives a white background. Without this filter the whole field appears reddened. It also serves to diminish the heat from the carbon arc.

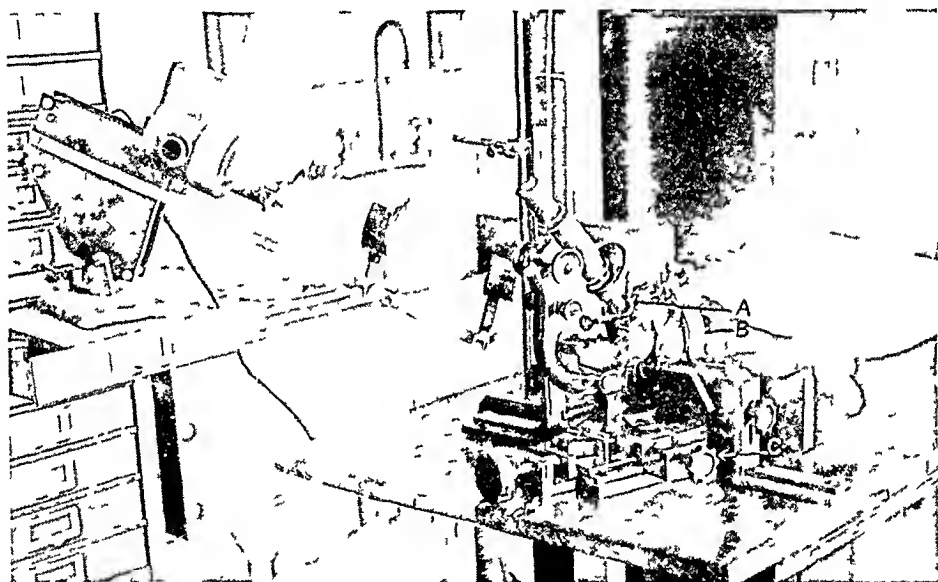


Fig 1—Forbes' apparatus set up 1. A, window in place, B, clamp for holding animal's head, C, mechanical stage carrying microscope.

With this apparatus a good exposure of the parietal region is obtained, the head of the animal is held steady over long periods, and the microscope can be readily adjusted to any desired field. In addition, by means of the window and by reason of the possibility of injecting or removing fluid through the needles from the interior of the cranium, pressure relationships are controlled, so that, so far as the pressure of the spinal fluid is concerned, conditions approach the physiologic. In the experiments the procedure was as follows:

Sodium amytal was used as the anesthetic in most instances, ether and ethyl carbamate (urethane) each having been used on one occasion. As a rule 50 mg of amytal per kilogram of body weight was employed, but, as the drug deteriorates after being made up for some time, larger doses were at times required. From

ten to fifteen minutes after the intraperitoneal injection of this amount of drug, warmed to the temperature of the body, the animal was usually anesthetized so that the operation could be started. To facilitate respiration while the head was in the clamp and to make possible artificial respiration in emergency, a tracheal cannula was first inserted. Following this the left carotid artery was dissected free and a large string placed about it in order that it might be easily found later.

The left parietal region was now exposed by removal of the skin and muscles, the head was firmly clamped in place and an opening made by trephine in the most convenient location exposed. As soon as the button of bone was removed, an occipito-atlantoid puncture was made, and from the cisterna magna from 1 to 2 cc of cerebrospinal fluid was removed. This drew the surface of the brain away from the opening and permitted the removal of small spicules of bone from the inner table immediately around the opening. The dura was now lifted by means of a needle and touched with a small cautery heated to a dull red. As soon as the dura was perforated, it was lifted away from the upper surface of the brain, except at points where small vessels united the two. These sometimes resulted in troublesome bleeding points, which, if touched with the cautery, could, as a rule, be easily controlled. The dura was lifted by means of small forceps and removed by means of the cautery at a little distance from the bony margin. Care had to be taken at all times to prevent bleeding. If there were any bleeding points in the cut edges of the bone, they had to be stopped with bone wax before the removal of the dura.

The window was then screwed into place, and through the hypodermic needles any trapped air was washed out with warm Ringer's solution. When all the air bubbles were out, the needles were tightly corked. The needle in the cisterna magna was connected with a glass manometer filled to 100 mm above the level of the former with Ringer's solution. The mechanical stage, with the microscope attached, was then fastened to the table, the light was focused on the window, and the set-up was complete.

In some of the early experiments an attempt was made to obtain readings of the blood pressure, but owing to the duration of the experiments it was found impossible to keep blood from clotting in the blood pressure apparatus. This attempt was therefore abandoned.

For photography a Leitz "micca" camera was used in some instances and the "makam" in others. With the latter much better detail was obtained.

It should be emphasized here that the animal received no physiologic care during the observations, and no asepsis was used in any of the procedures. However, inflammatory reaction was never marked, and even after ninety-six hours, in one case, the field was clear save for a slight blurring due to edema. As the blood pressure could not be followed by manometer, the general state of the animal was judged by changes in the speed of circulation in the exposed blood vessels. This is apparently a rather delicate means of estimating circulatory efficiency.

NORMAL APPEARANCES

The normal conditions were fully described by Forbes,³⁰ but in order to make clearer the changes taking place with the various experimental procedures the following brief description will be given.

The arteries and the veins stand out on a white, sometimes a slightly yellowish, background. The arteries are bright red, in contrast with the purplish red of the veins, so that the two can be readily identified. Occasionally in a large artery,

especially if it makes a sharp bend, there can be noticed a slight pulsation corresponding to the beat of the heart. As for the flow, in the arteries it is too swift to be seen until it reaches the fine arterioles, where rapid flow can sometimes be seen. In the veins, on the contrary, in all sizes, the flow can be seen. In the smaller ones, individual corpuscles are observed floating in the plasma. When the venules are followed into the veins, it is noticed that the stream line of the individual venule can be followed for a considerable distance before its identity is lost among the other inflowing streams. No definite capillary loops can be seen, but arterioles only large enough to admit red blood cells in single file can frequently be observed.

EXPERIMENTAL OBSERVATIONS

The experiments carried out have consisted of the injection of various types of foreign substances into the carotid artery of the cat and the observation of the effect of these on the blood vessels of the pia and on the rate of the blood flow over varying lengths of time. These observations were made by means of magnifications of 45 and 100. The number and the type of experiments reported may be seen by reference to the table.

Fat—Eighteen animals were used in observations of fat embolism. Cat fat, cottonseed oil, cream and an emulsion of cottonseed oil and of soap were used. In some of the experiments the fat was previously stained by the addition of a few crystals of sudan III or with a small amount of a 1 per cent aqueous solution of osmic acid. In some preliminary experiments the animals died, but none of these is included in the eighteen mentioned.

Nine experiments were carried out with unstained cat fat. The cat fat for this purpose was obtained by rendering the fatty tissue obtainable from the previously used animal. After being rendered it was put in the refrigerator and kept there until it was needed. Before being used, it was warmed until it just became fluid. The amount of this fat injected varied somewhat, but it was found that the optimal amount to yield a number of emboli without causing immediate death of the animal was about from 0.125 to 0.25 cc. The duration of these observations varied from three to fifty-six hours.

The other group of experiments included two with cottonseed oil, three with an emulsion of cottonseed oil, one with thick cream, one with cottonseed oil stained with osmic acid and two in which cat fat stained with sudan III was used. In general, the results obtained in the second group were analogous to those obtained with the fresh, unstained cat fat. Those of special interest will be noted later.

With the animal prepared in the manner described, the carotid was exposed and the fat injected slowly, care being taken that after

the point of the needle was in the artery, traction on the latter was released, so that the flow of the blood was not retarded by a kinking of the vessel. Soon after the injection was begun, fat droplets were

Table of Experiments

Cat	Date	Weight, Kg	Anesthetic	Material Injected	Amount, Cc	Duration
7	12/17/29	5.7	Amytal	Cottonseed oil	0.25	3¼ hr
8	12/11/29	3.3	Amytal	Cottonseed oil stained with osmic acid	0.125	12 hr
9	12/13/29	2.4	Amytal	Cat fat unstained	0.125	27½ hr
10	12/16/29	2.2	Amytal	Thick cream	2.5	3 hr
11	12/18/29	2.5	Amytal	Cottonseed oil emulsion	1.0	12 hr
13	12/23/29	2.0	Amytal	Cottonseed oil emulsion	0.125	7½ hr
14	12/30/29	2.0	Amytal	Cottonseed oil emulsion	0.5	3 hr
34	2/18/30	2.0	Amytal	Cat fat unstained	1.0	30 hr
35	2/20/30	2.7	Amytal	Cat fat unstained	0.125	24 hr
36	2/21/30	1.9	Amytal	Cat fat unstained	0.25	15 hr
37	2/22/30	1.9	Amytal	Cat fat unstained	0.25	12 hr
38	2/24/30	2.4	Amytal	Cat fat unstained	0.25	12 hr
39	2/25/30	3.0	Amytal	Cat fat unstained	0.2	56½ hr
44	3/10/30	3.2	Amytal	Cat fat unstained	0.5	49 hr
45	3/13/30	2.0	Amytal	Cottonseed oil	0.06	20 hr
46	3/14/30	1.5	Amytal	Cat fat unstained	0.09	34 hr
65	4/25/30	2.4	Amytal	Cat fat stained with sudan III	0.5	3 hr
66	4/26/30	3.3	Amytal	Cat fat stained with sudan III	0.5	9½ hr
1	11/15/29	3.0	Amytal	Animal charecoal	0.25	48 hr
2	11/19/29	2.5	Amytal	Animal charecoal	1.0	9¾ hr
3	11/21/29	2.7	Amytal	Willow charecoal	0.25	9½ hr
4	11/26/29	3.8	Amytal	Animal charecoal	1.0	4 hr
25	1/21/30	2.5	Fiber	Willow charecoal	0.25	9 hr
30	2/7/30	2.4	Amytal	Animal charecoal	0.5	24 hr
31	2/12/30	3.1	Ethyl carbamate (urethane)	Animal charecoal	0.5	6 hr
32	2/17/30	2.4	Amytal	Animal charecoal	0.5	4 hr
50	3/20/30	2.7	Amytal	Animal charecoal	0.5	36 hr
64	4/14/30	3.0	Amytal	Animal charecoal	0.5	4 hr
22	1/15/30	2.0	Amytal	Emery powder	1.0	5 min
26	1/24/30	4.6	Amytal	Emery powder	0.5	15 min
27	1/25/30	2.5	Amytal	Emery powder	0.5	10 min
30	1/30/30	3.7	Amytal	Glass powder	0.5	5 min
16	1/2/30	2.1	Amytal	Moist blood clot	0.25	96 hr
17	1/7/30	2.0	Amytal	Dry blood clot	1.0	28 hr
20	1/11/30	1.9	Amytal	Contaminated blood clot	2.0	1 hr
21	1/13/30	2.0	Amytal	Contaminated blood clot	0.5	28½ hr
24	1/18/30	2.1	Amytal	Contaminated blood clot	1.0	4 hr
15	12/31/29	2.1	Amytal	Air	2.8	8 hr
53	3/25/30	2.1	Amytal	Air	0.4	2 hr

seen passing along in the larger blood vessels. At first, these all passed out of sight, but as more came along, many of the smaller vessels were found to be plugged with fat. The larger droplets of fat seemed to have a tendency to pass by the smaller vessels until pressure became such as to force some of it into them. When a fat droplet became caught in a vessel it as a rule, plugged it completely.

The size of the blood vessels plugged varied with the amount of fat, the larger the amount injected, the larger were the vessels that were found blocked. With the smaller amounts the vessels blocked were usually small, emboli were frequently seen in vessels measuring from 12 to 14 microns in diameter.

After the lodging of an embolus, the size of the blood vessel in the case of the larger vessels was apparently unaltered. In the smaller arterioles there was often noted an apparent stretching of the wall of the vessel over the embolus (fig 2 *A* and *B*). The changes actually taking place could not be measured, however, as it was not known before the injection just which vessels would be the ones to be plugged. In

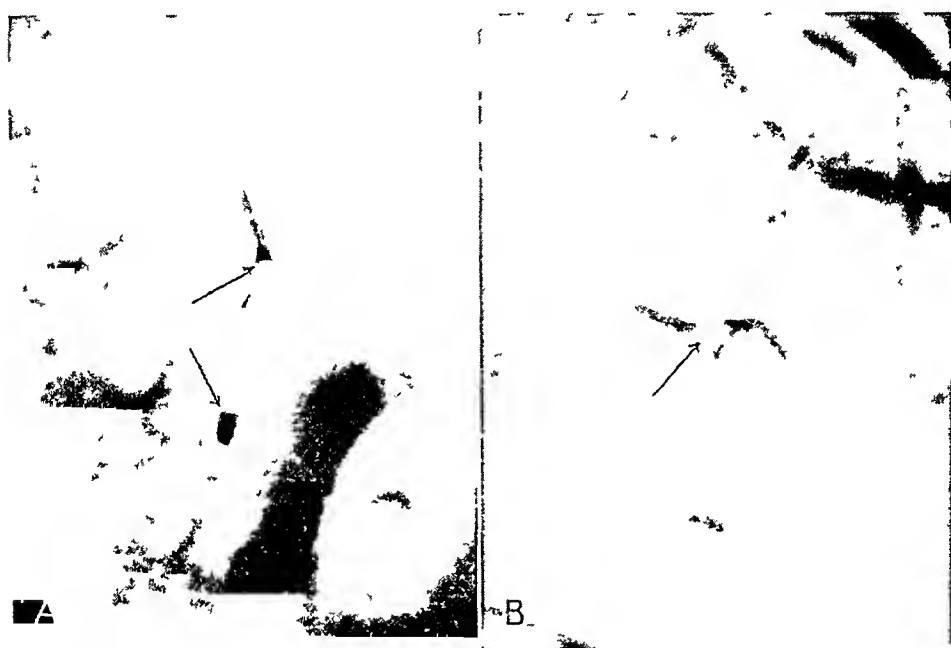


Fig 2—*A*, photomicrograph of a fat droplet lodged in an arteriole ($\times 80$). The photomicrograph was taken twelve hours after the injection of the fat. On each side of the embolus there is a short column of dark purple cells (indicated by arrows). There is a slight bulging of the vessel over the embolus. *B*, photomicrograph of a fat embolus ($\times 80$). A short column of dark blood cells can be seen on each side of the embolus.

none of the preparations were there any evidences of contraction either proximal or distal to the embolus. The blood column came up to and in contact with the end of the embolus, producing a stasis of red cells back to the next branch. At times in the larger vessels there was noticed a tendency for the red cells to creep up beside the fat, but it was never observed that a channel was reestablished in a vessel at first completely occluded. Frequently the stream from an unblocked vessel as it passed a branch which was occluded, would drive into the

latter with each pulse, and, a little at a time, sweep the trapped blood cells out until finally there was mostly plasma remaining, with only a few red cells close to the embolus. In spite of this marked stasis, no thrombosis occurred, though the vessel was plugged for as long as twenty-four hours. Although the majority of the fat emboli were driven, after several hours, into the substance of the brain and the circulation in the larger vessels was in many places reestablished, it seems impossible for some of the capillaries not to have become permanently plugged. It was not hoped to see these plugged, as they could not be seen before the injection, but it was expected that, should they become plugged, there would be produced small hemorrhages,

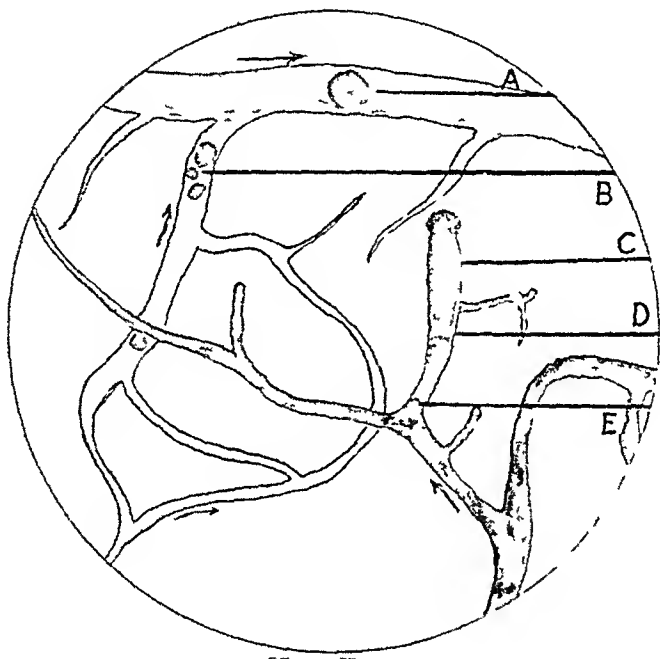


Fig 3—Free-hand sketch of fat droplets in arteries and veins. The letter *A* indicates a fat droplet with a small white thrombus about it in a vein, *B*, fat droplets in a venous branch, *C*, a fat droplet plugging an arteriole, *D*, trapped blood cells that have become deep purple, and *E*, bulging of the flowing stream of blood into the blocked branch. Note the thinning of the blood cells in the blocked portion of the vessel.

as these have been so frequently stressed as indicating fat embolism in the capillaries of the skin. Although hemorrhages were constantly searched for in all preparations, they were never found. The pial vessels may be peculiar in this respect, as hemorrhages were found in sections taken from the substance of the brain in some of the animals.

Fat was found in the form of small free droplets in the veins (fig 3) many times. The shortest time elapsing after the injection into the carotid before the appearance of fat in the veins was ten

minutes. It may have reached the venous side sooner than that, however, as attention was primarily focused on the arterial emboli. At times fat globules appeared in the veins singly or in pairs, often, however, large numbers at a time passed along in the veins, welling up from vessels of the cerebrum. At times these droplets became lodged in the veins, apparently for no reason at all, since the vessel was so much larger than the particle of fat. This, however, was probably due to the decrease in the power and speed of the stream as it recedes from the force of the arterial pulsation and reaches the broader veins. Many of them lodged at the point where an artery crossed over a vein, depressing somewhat the wall of the latter.

The picture of fat in the veins was particularly striking when fresh fat stained deeply with sudan III was used. Large yellow droplets could be seen in the veins, and on close examination it was found that there were somewhat irregular white haloes about these droplets, and that on the distal side (in reference to the blood current) there were formed small white thrombi. Although these were much smaller than those seen with charcoal (to be described in later paragraphs), they could be seen breaking off and being carried away from time to time.

Although, as stated, the fat droplets, as a rule, plugged completely the vessels on the arterial side in which they lodged, several instances were seen in which this did not occur. One of these was particularly interesting. In a fairly large-sized vessel several droplets of fat were lodged, but in such a way that blood continued to flow by them. About the distal one white thrombi were being formed, and these could be seen breaking off and being carried away, just as will be described in the case of charcoal emboli.

In the experiment in which thick cream was used, only a few emboli were found in the pial vessels, even after the injection of 2.5 cc. During the injection, however, the cream could be seen coursing through, so that it was known to have passed the blood vessels, and not to have been blocked from some cause lower in the course of the artery. On section many emboli were found in the brain substance.³²

A typical protocol of this series of observations follows:

Cat 9, weighing 2.4 Kg., was employed for the experiment

Dec 3, 1929

10 10 a m	17 cc amytal (1 per cent) is given intraperitoneally
10 20 a m	Operation is started
11 20 a m	Operation is over

³² The brains from all the experimental animals were saved and studied. The pathologic effects at the end of the various lengths of time will be reported later.

- 11 30 a m Unstained cat fat, 0.125 cc, warmed until it becomes fluid is injected into the left carotid
- 11 31 a m Large fat droplets are seen coursing through the medium-sized arteries, lodging in the arterioles and completely blocking the blood flow. There is a slight oscillatory movement of the blood in the blocked vessels, but no blood is found going past any of the emboli
- 11 50 a m Large fat droplet is found in a vein
- 12 05 p m Many fat droplets are seen in the veins. Veins are much larger apparently than the drops of fat, but the latter cling to the wall of the vessels, while the blood flows around them
- 12 10 p m One arteriole contains a long fat embolus, distal to the embolus is a clump of cells, of deep purplish color, proximal to the embolus there is mostly plasma with a few red cells in it. This is not clotted, as the red cells float to and fro
- 12 30 p m Cells, deep purple, are noticed working up beside the embolus
- 1 30 p m Embolus is being pushed along a little further. Many fat droplets are seen in the veins
- 7 00 p m Very little change is observed. Embolus has been pushed a little further, but it still completely blocks the vessel, though red cells are still present along one border
- 10 00 p m No change is observed
- Dec 4, 1929
- 9 00 a m No change is observed
- 11 00 a m No change is observed, no hemorrhages are found
- 1 30 p m Circulation is weaker, fat has possibly been pushed a little further
- 3 00 p m Cat is found dead. No hemorrhages have been noticed at any time about the vessels exposed through the window

Charcoal—Ten animals were used in observations of charcoal embolism. Very finely powdered charcoal was used, animal charcoal in eight animals and willow charcoal in two. There were no apparent differences between the observations in experiments in which animal charcoal was used and those in which willow charcoal was used. To determine whether the result would be different with various anesthetics, ether and ethyl carbamate (urethane) were each used in one experiment. No significant alterations in reaction occurred. Consequently, as amytal was more convenient under the experimental conditions, this was the anesthetic thereafter employed. The time of coagulation was determined in several of these animals, and no alteration was found.

For obtaining emboli with charcoal a small amount of the powder was mixed with approximately from three to four times its volume of Ringer's solution, and a small amount of this suspension, usually about 0.5 cc, was injected into the left carotid of an animal, prepared as described. As the number of emboli obtained varied with the different suspensions, the field was watched with the low magnification and when a number of emboli had been obtained, the injection was stopped.

Within a few moments after the injection was started, particles of charcoal could usually be seen in the pial blood vessels. Some of these were carried by the blood stream on through the exposed field and out of sight, others were found lodged in vessels of various sizes, depending somewhat on the size of the particles injected. Some of the emboli caused a complete blocking of the vessels in which they lodged. This might be permanent, or the embolus a little later might be swept on, leaving no evidence of injury to the wall of the vessel. For the most part, however, when the vessel was completely plugged, the embolus was not dislodged, but blood could be seen coming up to and in contact with the embolus.



Fig 4—A, photomicrograph of a charcoal embolus ($\times 80$). The white thrombus about this embolus is easily seen. The blood continues to flow past it. B, photomicrograph of a charcoal embolus ($\times 80$). There is no evidence of any formation of a thrombus about this embolus.

Other emboli were observed to be located in a perfectly white field, apparently having no connection with the circulation. This might possibly have been caused by a contraction of the blood vessel in which such particles had lodged, with the consequent expulsion of all the blood from each side, or it might have been due to the action of plasma. As previously noted, the blood cells in the proximal portion of a blocked vessel might be washed out by the action of the current in the vessel from which it branched. It seems possible that later the plasma thus left in this portion of the vessel may have passed by the embolus to displace the cells in the distal portion.

Soon after the lodging of a particle of charcoal which did not completely occlude the blood vessel, there appeared on the surface of the embolus a small white thrombus. This at times reached a size easily seen, at other times it was perceptible only by careful examination (fig 4 *A* and *B*). This thrombus might complete the occlusion of the vessel.

This thrombus frequently did not occlude the blood vessel, and it is this fact which is of special interest. Blood continued to flow for hours past an embolus of rough charcoal that had become stuck in a small vessel, and this in spite of the fact that the stream was often much slowed on account of the number of emboli present.

If the thrombus did not occlude the blood vessel, it increased very slowly in size, except in the direction of the blood stream or, in other words, distal to the embolus. There it grew more rapidly, clung to the embolus, swinging to and fro in the stream, and finally was broken

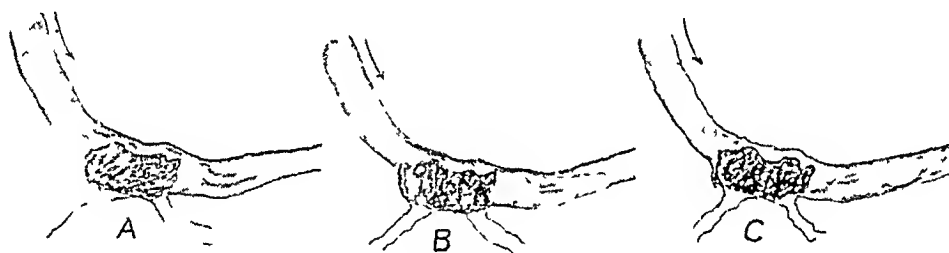


Fig 5—Camera lucida drawings of a foreign body embolus ($\times 80$), showing successive stages in the formation of a platelet embolus. At first there is a thin, white thrombus, which can be seen waving from side to side in the blood stream distal to the embolus. This gradually increases in size and finally becomes so large that it is broken off and swept away.

off and carried away (fig 5). This process might be repeated over and over, with apparently little or no hindrance to the flow of blood. In one experiment there were three rather large emboli caught in a vessel, only a little distance apart. In spite of the size of the emboli and the slowing of the stream which they produced, the blood continued to flow past them for hours.

Observations were made over periods varying from four to forty-eight hours. In all of these there were to be found emboli past which blood was found flowing until the death of the animal or until the experiment was ended. Although the majority of the emboli were caught in larger blood vessels, some were found occluding small ones, yet no hemorrhages were seen about any of them.

A typical protocol follows

Cat 30-a, weighing 24 Kg, was used in this experiment

Feb 7, 1930

- | | |
|-----------|---|
| 9 00 a m | 16 cc 1 per cent amytal is given intraperitoneally |
| 9 15 a m | Operation is started |
| 10 15 a m | Operation is completed, and animal is ready for injection of suspension |
| 10 50 a m | Small amount of suspension of animal charcoal is injected into left carotid |
| 10 51 a m | Many emboli are present Some of these are found completely blocking the vessel in which they have lodged In some cases, the stream is apparently not much affected, in others, it is slowed |
| 10 55 a m | An embolus is found in an arteriole, the width of the embolus apparently equal to the diameter of the lumen of the vessel, stream in this region is somewhat slower than normal, no contraction of the vessel is apparent A white thrombus is present, some being broken away from the peripheral portion from time to time |
| 11 30 a m | Circulation continues past the embolus There is no apparent increase in the size of the thrombus, although white thrombi are still forming and being broken away |
| 2 00 p m | No change is observed |
| 3 00 p m | Photograph of embolus is made |
| 9 30 p m | No change is noted Cat is wrapped and left for the night |

Feb 8, 1930

- | | |
|-----------|--|
| 9 30 a m | Circulation is weaker Blood continues to flow past the embolus |
| 11 00 a m | Blood still flows past the embolus The entire circulation is somewhat weaker, and the stream past the embolus is also somewhat retarded A second photograph is taken of the same embolus and the cat is killed The duration of observation of the one embolus was twenty-four hours, during which it had not shifted its position, nor had it occluded the lumen, though the piece of charcoal was large compared to the size of the vessel (fig 6 <i>A</i> and <i>B</i>) |

Emery and Powdered Glass—Four cats received injections of emery and powdered glass, three received injections of emery and one of powdered glass For the injections of emery a small portion of commercial powdered emery was placed in a mortar and ground until a very fine powder was obtained To this was then added about from three to four times its volume of Ringer's solution, and the mixture was stirred vigorously It was found that, despite considerable grinding, it was difficult to get the powder fine enough to remain in suspension Trouble was also encountered when an attempt was made to inject it as the small particles of emery would get between the plunger and the barrel of the syringe and cause it to stick A suspension having been prepared by vigorous stirring, a small portion was drawn into the

syringe and quickly injected. Because of these difficulties it was impossible to inject a measured amount.

The three animals given injections of portions of this suspension died within a few minutes after the injection. In the blood vessels could be seen long wormlike strings of white thrombi waving in the rapidly failing blood stream. At times red blood cells were caught in them. These thrombi occasionally appeared to be attached to the walls of the vessels moving backward and forward with each cardiac pulsation. Following the death of the animal there was always noticed a congestion of the pial vessels instead of the blanching seen following death from other types of emboli.

The same difficulties were encountered when it was attempted to inject powdered glass. The single cat into which a small amount was



Fig 6—*A* photomicrograph of a charcoal embolus four hours after injection. *B* the same embolus twenty-four hours after injection ($\times 60$). This illustrates the continued flowing of blood past an embolus apparently large enough to block the vessel completely.

injected lived only a short time, the blood vessels being rapidly filled with thrombi.

Blood Clot—The experiments with blood clot were designed to see whether the previous presence of elements of coagulation would cause an increase in the speed of thrombosis. Five cats were used. Three different types of material were used. As only one of each type was satisfactory, these three alone will be reported on, one in detail, the other two in summary. As will be seen, the results with all of these were very similar to those obtained with charcoal.

Cat 16, weighing 21 Kg., was used in one of the experiments. The clot from 5 cc. of blood which had been obtained from a cat forty-eight hours previously and had been kept on ice was removed from its serum, placed in a mortar and ground until it could be passed through a no. 20 Luer needle. In order to facili-

tate injection a little of its serum was added to the ground clot The protocol follows

Jan 2, 1930

- 10 38 a m 10.5 cc of 1 per cent amytal is given intraperitoneally
- 10 48 a m Operation is started
- 11 55 a m Operation is completed
- 12 00 m 0.25 cc of blood clot is injected into the left carotid Immediately after the injection, many fibrin emboli are seen in the arteries As the field is watched, emboli lodge, the flow is reversed, another lodges in another vessel, and the first is swept away This shutting and opening up of channels continues
- 12 03 p m Many white thrombi are seen in the veins, some large
- 12 30 p m White emboli continue to lodge about in the vessels
- 1 00 p m All the arteries seem apparently clear of emboli, with the exception of two vessels In each of these two, at a point where it branches (fig 7), is lodged a large white embolus, from three to four times as long as it is wide The flow of the blood past it is impeded, but is still fairly brisk
- 2 00 p m The flow about the two emboli continues No other emboli are found
- 9 30 p m No other emboli are found The flow in the lower branch of one of the arteries containing an embolus is stopped
- 9 40 p m Stream is going past the embolus in both branches of artery in which at 9 30 flow in lower branch was stopped, the flow is continuing uninterrupted past the embolus in the other artery shown in figure 7

Jan 3, 1930

- 9 00 a m The flow past both emboli is about the same, the animal is in good condition
- 12 25 p m The animal is restless, it is given 5 cc amytal intraperitoneally The flow continues the same
- 2 30 p m Some edema of the pia is observed The circulation is apparently not changed by the emboli
- 9 45 p m The circulation continues good, and the blood continues to flow past the obstructions with the same speed as was noted twenty-four hours previously The animal, not deeply anesthetized, responds to stimulation actively
- 10 00 p m The animal is somewhat restless, 5 cc of amytal is given intraperitoneally

Jan 4, 1930

- 8 30 a m The circulation is unchanged
- 10 00 a m No change is seen
- 12 30 p m The blood flows strongly past the emboli
- 11 00 p m The right hind leg is spastic, no change in circulation is seen

Jan 5, 1930

- 10 00 a m The circulation is the same
- 11 30 a m No change is seen
- 11 45 a m The circulation is still strong
- 4 00 p m No change is seen
- 6 00 p m No change is seen
- 11 30 p m No change is seen

Jan 6, 1930

- 9 00 a m The circulation is much weaker, but the blood is going past the emboli. There is no apparent increase in size in the surrounding thrombi.
- 9 30 a m No change is seen.
- 12 00 m The circulation is weaker, but the flow continues past both emboli. The animal is killed. The duration of observation has been ninety-six hours.

In another experiment with blood clot a suspension of dried blood clot was used. Blood obtained from one of the animals previously used was allowed to dry on a piece of filter paper. After drying it was broken into small pieces, put in the mortar and ground until a fine powder had been made. A small amount of this ground, dried clot was mixed



Fig 7—A blood clot embolus, past which the blood continued to flow for ninety-six hours

with about three times its volume of Ringer's solution just a few minutes before the injection was made.

The animal having been prepared in the usual manner 1 cc of the described suspension was injected into the left carotid. After the injection brown emboli could be seen in the small pial blood vessels. Some of these completely occluded the vessels in which they lodged, while others did not. In one field there was an embolus which was lodged in a small vessel just proximal to a point where it branched. Past this embolus the flow was intermittent, sometimes going briskly and at other times being completely blocked. The animal was killed at the end of twenty-eight hours and at this time the blood was still intermittently flowing past the embolus.

In a third experiment a cat received 0.5 cc of a suspension composed of ground dried blood clot mixed with 2 cc of a forty-eight hour broth

culture of a hemolytic streptococcus and 1 cc of Ringer's solution. Many emboli were seen following the injection. As these lodged there was noticed the formation of white thrombi about them. The amount of secondary thrombosis was, in some instances, sufficient to stop the flow of blood. In one portion of the field there was noticed a large brown embolus caught at the bifurcation of a fairly large artery. On this embolus white thrombi formed, and the flow in both branches was stopped. However, within a short time blood was found flowing again in both branches. This flow continued until the animal was killed, twenty-eight and a half hours after the injection was made.

Am —Since the results obtained in the two experiments with air are analogous, a protocol of one only will be given.

Cat 15, weighing 2 Kg, was used in this study.

Dec 31, 1929

- | | |
|-----------|--|
| 10 00 a m | 10 cc of 1 per cent amytal is given intraperitoneally |
| 10 15 a m | Operation is started |
| 11 00 a m | Operation is completed, and 0.2 cc of air is injected into the left carotid. Almost immediately bubbles of air are seen in the larger arteries, moving swiftly along, and within a short time they have passed out of the field, leaving it clear. No contraction of the vessels is noticed as the air passes along. |
| 11 02 a m | 0.2 cc of air is injected. The larger arteries are filled, some retaining the bubbles for a short time, but these are soon cleared. This time a number of the smaller vessels are also filled with air, but with each pulse the air is pushed a little further along the vessel and soon the field is practically clear. The blood column comes in contact with the air in a manner very similar to that in the case of the fat emboli, and the meniscus is of the same shape. |
| 11 15 a m | No emboli are present. |
| 11 16 a m | 0.2 cc of air is injected, with this injection practically every visible artery is filled with air. The air is being pushed along, however, with each impulse. |
| 11 30 a m | Only two small emboli found in the entire field. No air has as yet been observed in the veins. |
| 11 50 a m | 0.4 cc of air is injected. Many vessels are filled. |
| 12 50 p m | All emboli are gone from the field. |
| 1 50 p m | 0.2 cc of air is injected. Many of the smaller vessels and a few of the larger ones are filled with air. |
| 2 30 p m | The field is clear of emboli. |
| 2 40 p m | 0.4 cc of air is injected. Every artery in the field is emptied of blood. |
| 3 35 p m | No emboli are found anywhere. |
| 3 40 p m | 0.4 cc of air is injected. Many emboli are seen. |
| 4 00 p m | The field is clear of emboli. |
| 4 05 p m | 0.4 cc of air is injected. Many emboli are seen, the field is blanched. |
| 4 50 p m | The field has just cleared. |

5 00 p m	0.4 cc of air is given. The vessels are blanched. Spasticity of the right fore leg is noticed, and convulsive motion in the left leg.
5 30 p m	The field is clear, except for a few small vessels in one quadrant.
5 45 p m	The field is entirely clear.
7 00 p m	The circulation is very strong, the field is clear of emboli. No air has been seen at any time in the veins. The animal is killed.

COMMENT

By direct observation of the pial blood vessels it was seen that fat emboli, produced by injection of fat into the carotid artery of the cat, completely blocked, as a rule, the vessels in which they lodged. Most of the fat, within a relatively short time, was pushed into the substance of the brain if too large an amount had not been injected. Some of the fat traversed the capillaries and in some instances, could be found in the veins within ten minutes after the injection.

Owing to the usual complete plugging of the arterial vessels when fat lodged in them there was little opportunity for the study of white thrombi about them. However, in one instance the arterial stream was seen passing several small fat droplets. The stream at this point was slowed so that the individual cells could be seen. Under these conditions it was observed that white thrombi formed about the distal fat droplet and were from time to time broken off and carried away.

On the fat droplets seen in the veins especially on those stained with sudan III, small white thrombi could also be seen. These always remained small, and the masses that were given off from time to time were also small. None of the veins was ever found blocked with a thrombus developed on fat droplets although at times a number of them were present behind a small artery where it crossed a vein.

In none of the experiments were hemorrhages noted, although small blood vessels were often blocked. This was unexpected, as petechial hemorrhages have often been noticed in the skin following fat embolism. Cohn³³ in 1860, found numerous hemorrhages on the surfaces of the brains of dogs receiving intracarotid injections of various substances.

The results obtained following the introduction of charcoal were particularly interesting. It was seen that a rough particle of carbon might become caught in a blood vessel, and whereas white thrombi formed and were carried away from time to time, the stream might continue to flow past the obstruction for as long as twenty-four or forty-eight hours.

33 Cohn, B. Klinik der embolischen Gefasskrankheiten. Breslau 1860.

Very analogous and even more surprising were the similar observations made when coagulated blood was used as an embolus. Past such an embolus circulation continued in one instance for ninety-six hours. In other words, the growth of a thrombus about an embolus was not continuous and progressive under all circumstances. If as may be presumed, the thrombus formed to separate the possibly harmful foreign body from the blood stream, the formation of the thrombus, in these experiments, practically ceased when this end was attained. Only when more noxious foreign bodies, such as those that injured the vascular wall, were present, was the process at all progressive. In view of the

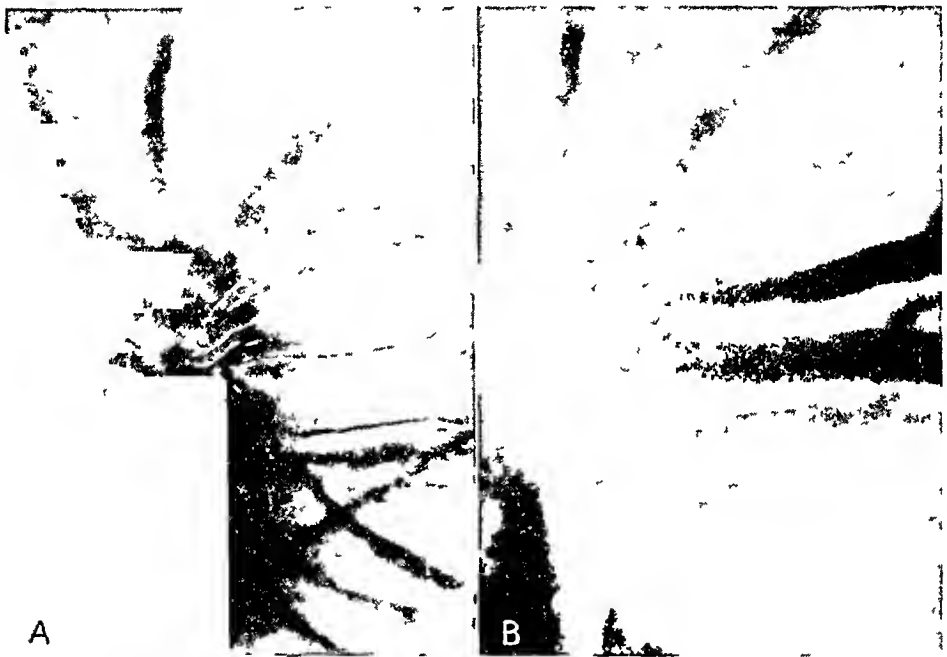


Fig 8—*A*, photomicrograph of pial blood vessels (reduced from a magnification of 100) a few minutes after the injection of 0.4 cc of air. The circulation is completely stopped. *B*, photomicrograph of the same field as that shown in *A*, one hour after the injection of air. The circulation is completely reestablished.

ordinary conception of coagulation of the blood—that it starts on contact of blood with damaged tissue and previously formed clot—it seems particularly interesting that formation of a thrombus ceased in this manner even when coagulum was used as the embolus. This observation emphasizes the distinction made by the earlier writers between a thrombus formed of platelets and fibrinous coagulation.

With emery and powdered glass extensive thrombosis developed rapidly, with death occurring in a short time after the injection. This was undoubtedly due to the injury of the endothelium which the passage of the sharp particles over it produced. As a result of this injury,

thromboplastic substances were liberated which caused the formation of extensive thrombi. These were readily seen in the blood vessels.

In the experiments in which air was injected, there was never noticed the retention of the air or the contractions observed by Jacobi and Magnus. On the contrary, the air was soon seen to disappear, whether entirely by absorption or partly by being pressed through the capillaries (fig. 8). It should be noted here again that in the experiments of Jacobi and Magnus the brain was not protected from expansion, and that this may account for the differences in observations. Van Allen³⁴ and his co-workers, by using a specially devised air trap and making the blood incoagulable by means of hirudin, were able to demonstrate air in the superior vena cava one and one-third minutes after it had been injected into the pulmonary vein.

These experiments showed that platelets collect on and about foreign bodies even if the surface is smooth. After the thrombus is initiated its growth is very slow, in an otherwise healthy animal, even in the presence of a retarded flow of blood. In cases in which there is extensive injury to the vascular wall there is widespread thrombosis. It may be concluded, therefore, that though the formation of a thrombus is readily initiated by the introduction of a foreign substance, the growth of such a thrombus may be very slow in the absence of injury to the endothelium. This in turn suggests that thromboplastic substance is liberated to much less extent by injury to the cellular elements that make up white thrombi than by injury to the vascular wall. In practically all of the previous studies of thrombosis there was present, in addition to the foreign body, some injury to the lining endothelium.

SUMMARY

Fat droplets in the arteries of the pia, in the vast majority of instances, completely blocked the vessels in which they lodged.

When injected into the carotid artery, fat was carried in large quantities through the pial blood vessels into the substance of the brain. It sometimes traversed the capillaries and was found in the veins within ten minutes after the injection. Occasionally some of the fat lodged in the pial arteries and remained there for a considerable period.

White thrombi formed on fat droplets, but to a less degree than on other types of foreign bodies.

The thrombi produced by rough and irregular pieces of charcoal were frequently insufficient to block the blood vessels in which they lodged,

³⁴ Van Allen, C. M., Hrdina, L. S. and Clark, J. Air Embolism from Pulmonary Vein. *Arch Surg* **19** 567, 1929.

even when present over a long period of time and when there was marked slowing of the blood stream

Sharp substances, such as emery and powdered glass, produced extensive thrombosis and death in a short time

Contrary to my expectations, blood clot emboli, moist, dry or highly contaminated, did not produce obstructive thrombosis, in some instances when observed as long as ninety-six hours

After numerous repeated injections of small amounts of air the pial circulation remained apparently uninjured

No hemorrhages were observed in relation to emboli of any nature in periods of observation as long as ninety-six hours, irrespective of complete or incomplete vascular occlusion

CONCLUSIONS

Following embolism in the cat the first reaction that occurs is the separation of the foreign body, no matter what its nature, from the blood stream by a collection of platelets, a "white thrombus," which is extremely friable and breaks off easily. The formation of this thrombus practically ceases when separation of the foreign body from the blood stream has been accomplished. If the endothelium has been injured by the foreign body, progressive thrombosis occurs. The distinction between these two processes probably lies in the freeing of thromboplastic substances in the latter instance. When progressive thrombosis does not occur, the external surface of the white thrombus is apparently entirely bland, so that the blood continues for many hours to flow past the obstruction, even when the space between the embolus and the opposite vascular wall barely admits a single erythrocyte. The effect of slowing of the blood current on this process—namely, the exteriorization of foreign bodies from the active blood current—is not perceptible. If not originally large enough to occlude the blood vessel, the white thrombus, in general, does not grow large enough to do so even in the presence of a failing blood stream or when bathed in blood that flows only intermittently. This last observation is contrary to all previously reported opinions.

In the pia no perivascular reaction to vascular occlusion can be observed.

EFFECT OF EMETINE ON CARDIAC MUSCLE^{*}

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Many observers of the action of emetine have concluded that the drug is a general protoplasmic poison with particularly harmful effects on the heart. While the histologic results of its action on cardiac muscle have been studied they do not seem to have been reported in sufficient detail to command the attention that they deserve. Furthermore pictorial representations of the lesions described do not seem to have been published.

Podwyssotzki¹ working with what was probably impure emetine, first noted cardiac arrhythmia in laboratory animals following its use. With the drug in reasonably pure form, Wild² observed weakening, slowing and diastolic arrest of the heart and assumed that the drug acted as a muscle poison. Cardiac paralysis as the cause of death in animals poisoned by emetine was suggested by Lowin.³ In electrocardiographic studies on dogs given 4-18 mg. of emetine hydrochloride per kilogram intravenously, Levy and Rowntree⁴ noted ventricular fibrillation followed by an abrupt fall in blood pressure with death from acute cardiac dilatation. Pellini and Wallace⁵ stated that the chief toxic effects of the drug are exercised on the gastro-enteric tract and

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^{*} From the Pathological and Pharmacological Laboratories of the University of California Medical School.

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1 Podwyssotzki. Beiträge zur Kenntnis des Emetine. Arch. f. Exper. Path. u. Pharmacol. **11**: 231, 1879.

2 Wild, R. B. The Pharmacology of Ipecac Alkaloids. Lancet **2**: 1274, 1895.

3 Lowin, C. Beiträge zur Kenntnis der Ipecacuanha, Arch. Internat. Pharmacol. et Therap. **11**: 9, 1902-1903.

4 Levy, R. L. and Rowntree, L. G. On the Toxicity of Various Commercial Preparations of Emetine Hydrochloride. Arch. Int. Med. **17**: 420, 1916.

5 Pellini, E. F. and Wallace, G. B. The Pharmacology of Emetine, Am. J. M. Sc. **152**: 325, 1916.

on the heart. Death following intravenous injection was ascribed by them to cardiac paralysis, but death following large subcutaneous doses (150 mg per kilogram in cats) they held to be due to respiratory and cardiac failure. After small subcutaneous injections, death was considered due mainly to gastro-enteric changes, although the heart was congested at necropsy. Detailed pathologic studies were not reported. Lake⁶ observed fibrillary contractions of the heart in rabbits dying from lethal doses of the drug given intravenously, but no gross changes at necropsy, except edema of the lungs. On subcutaneous injections, hemorrhages in the lungs, congestion of the intestines, fatty changes in the liver and tubulonephritis were described. No observations of the heart were given. In the fatal case in man reported by Bais,⁷ marked degeneration of the heart muscle was found at necropsy. Arrillaga and Guglielmetti⁸ concluded that emetine may be considered a cardiac poison. In animals they observed auriculoventricular dissociation and auricular fibrillation. Chopra and Ghosh⁹ emphasized weakening of cardiac action following the therapeutic use of emetine, and also observed experimentally that death may result from auricular or ventricular fibrillation. Chopra, Ghosh and De¹⁰ noted in rabbits poisoned by emetine that "the parenchyma of the heart muscle is one of the earliest to be affected, the changes being (a) cloudy swelling of the muscle fibers and disappearance of transverse striation, (b) shrinking of the muscle fibers and (c) atrophy of fibers and their replacement by connective tissue cells. These may be the cause of some of the cardiac symptoms which occur in the course of injections in patients." Young and Tudhope¹¹ administered lethal amounts of emetine in divided daily doses to rabbits and guinea-pigs. The animals died in from five to twenty days, depending on the amount of the daily dose. In the pathologic studies, the authors described hyperemia and granular and cloudy swelling in the heart muscle, skeletal muscle, kidneys and liver, together with wallerian degeneration in occasional fibers of the sciatic

6 Lake, G. C. On the Toxicity of Emetine Hydrochloride with Special Reference to the Comparative Toxicity of Various Market Preparations, *Bull* 113, Hyg. Lab. U. S. Pub. Health Service 1916, vol 2, p 41.

7 Bais, W. J. Dood door Emetine. *Geneesk tijdschr v Nederl Indie* **61** 500, 1921, quoted by Findlay, G. M. Recent Advances in Chemotherapy, Philadelphia, P. Blakiston's Son & Company, 1930, p 81.

8 Arrillaga, F., and Guglielmetti, J. Action du chlorhydrate d'emetine sur le coeur, *Compt rend Soc de biol* **85** 596, 1921.

9 Chopra, R. N., and Ghosh, B. N. The Therapeutics of Emetine, *Indian M Gaz* **57** 248, 1922.

10 Chopra, R. N., Ghosh, B. N., and De, P. Toxicity of Emetine, *Indian M Gaz* **59** 338, 1924.

11 Young, W. A. and Tudhope, G. R. The Pathology of Prolonged Emetine Administration, *Rev Soc Trop Med & Hyg* **20** 93, 1926.

nerve and chromatolysis in a few of the anterior horn cells. Emetine was considered by them to be a general protoplasmic poison acting equally on all tissues. Death was ascribed to heart failure. Anderson and Leake¹² noted that emetine hydrochloride in single doses by mouth caused death within from two to eight days in more than 50 per cent of rabbits and cats given from 15 to 20 mg. of the drug per kilogram of body weight. Animals dying from lethal doses of emetine exhibited very extensive injury to warrant further pathologic study.

Tabled Summary of Experiments with Pathologic Changes

Animal	Dose of Emetine Hydrochloride per kg.	Manner of Death	Pathologic Changes
P 1	1,910	None	At 24 hr. postmortem, normal heart and lungs
P 2	3,910	None	At 24 hr.
P 3	1,910	Died in 24 hours	Small infarct in lungs with an embolus (artery only occluded)
P 4	2,910	Died in 48 hours	Infarct in lungs with an embolus (artery only occluded)
P 5	2,910	Died in 48 hours	No gross changes observed
P 6	2,750	Died in 2 days	Coronary artery occluded by a thrombus (embolus)
P 7	2,250	Killed in 4 days	Swelling of muscle cells and nuclei; atrophy of sarcomeres with a substantial proliferation of nuclei on sarcomeres. Absorption nuclei on all sarcomeres in heart
P 8	2,220	Killed in 4 days	Cardiac infarct as in P 6. No gross pathologic changes found
P 9	2,620	Killed in 11 days	Parefaction of heart muscle, swelling of cytoplasm and nuclei, atrophy of heart muscle fibers with loss of intercalated disc
P 10	3,050	Died in 10 days	Small relative cellular scars in heart muscle, surrounding atrophic and necrotic muscle fibers, general swelling of heart muscle fibers and nuclei and incomplete hyaline coagulation of cytoplasm, necrosis of fibers in section of skeletal muscle

* By injection of 5 cc. of air into ear vein

† Two divided doses of 5 mg. per kilogram each within four days

‡ After last dose

§ Three divided doses of 5 mg. per kilogram each within eight days

EXPERIMENTAL TECHNIC

Normal adult rabbits were given the powdered drug in gelatin capsules. All animals were kept singly in wire cages under identical conditions of diet hygiene and temperature, and were observed for a period of fifteen days unless death occurred. Those dying within this period were immediately submitted to postmortem examination, and portions of representative tissues were taken for histologic examination. The nervous system was not included in this study. Three animals were killed by the intravenous injection of air in order to obtain material unaltered by postmortem changes. Untreated animals were maintained in the labora-

¹² Anderson, H. H., and Leake, C. D. The Oral Toxicity of Emetine Hydrochloride and Certain Related Compounds in Rabbits and Cats. *Am J Trop Med* 10 249, 1930

tory under similar conditions as controls, and two were killed by the intravenous injection of air to obtain "normal" tissue for comparative study. Zenker's fixation was used, and sections were cut at from 4 to 8 microns and stained with hematoxylin and eosin.

Details of the experiments, with an abstract of the pathologic observations, are recorded in the table. All animals received single doses of emetine hydrochloride, except two. R-308 was given three doses of 5 mg per kilogram at four day intervals, and R-309 was given two doses of 5 mg per kilogram four days apart. Two control animals, R-301 and R-310, received no drug and were killed by the injection of 5 cc of air into the ear vein. Photomicrographs of histologic sections of cardiac tissue of untreated and animals poisoned by emetine are shown in figures 1 to 5.

PATHOLOGIC OBSERVATIONS

Morphologic evidence of the effect of lethal or sublethal doses of emetine hydrochloride on the heart muscle in rabbits was not imme-

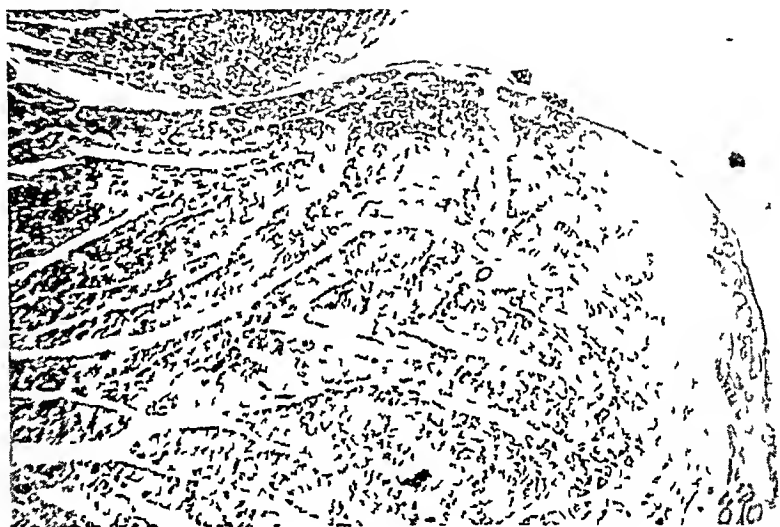


Fig 1 (rabbit 301)—Heart muscle of a normal rabbit, showing closely grouped small fibers with inconspicuous nuclei. Note entire absence of interstitial proliferation. Magnification, $\times 175$.

diately apparent. Rabbits (R-303 and R-304) dying from twenty-four to forty-eight hours after a lethal dose of the drug showed little or no histologic change in the muscle fibers. These were spread apart, due presumably to interstitial edema. This was considered a secondary phenomenon in a heart that had failed, rather than a primary condition. Figure 1, representing a section of the heart muscle of an untreated rabbit, shows the normal compactness of the muscle fibers. In rabbit 299 (fig 2), killed three days after receiving 20 mg per kilogram, the interstitial tissue was readily seen to be unduly prominent. Numerous foci were apparent in which the interstitial cells exhibited proliferation in response to, and replacing degenerated and necrotic muscle fibers. A few polymorphonuclear neutrophils, numerous eosinophils and plasma

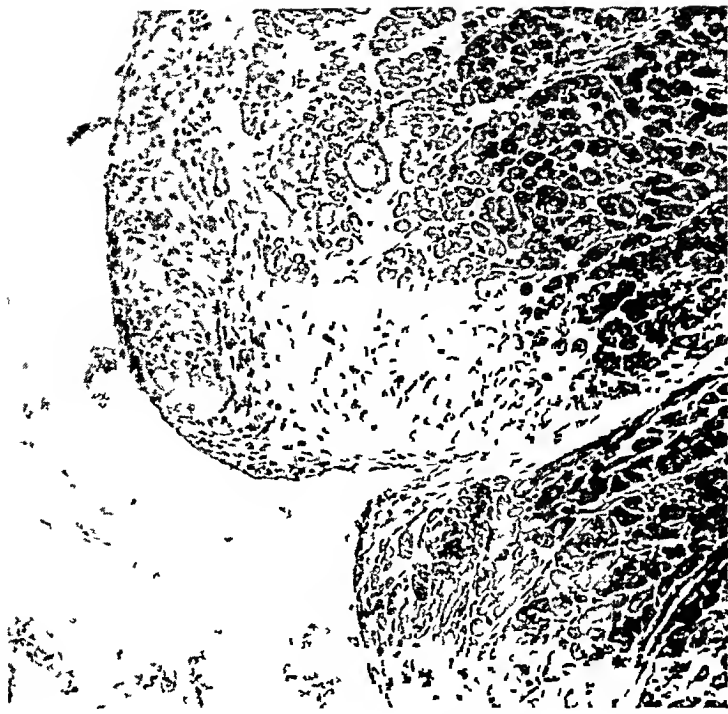


Fig 2 (rabbit 299) —Proliferation of the interstitial tissue of heart muscle in response to myocardial damage. A conspicuous focus of cells is seen just beneath the endocardium, which is shown in greater detail in figure 3. The hypertrophy of muscle fibers and nuclei considered an indication of injury will be clearly seen if this photomicrograph is compared with that of normal muscle in figure 1. Magnification, $\times 175$

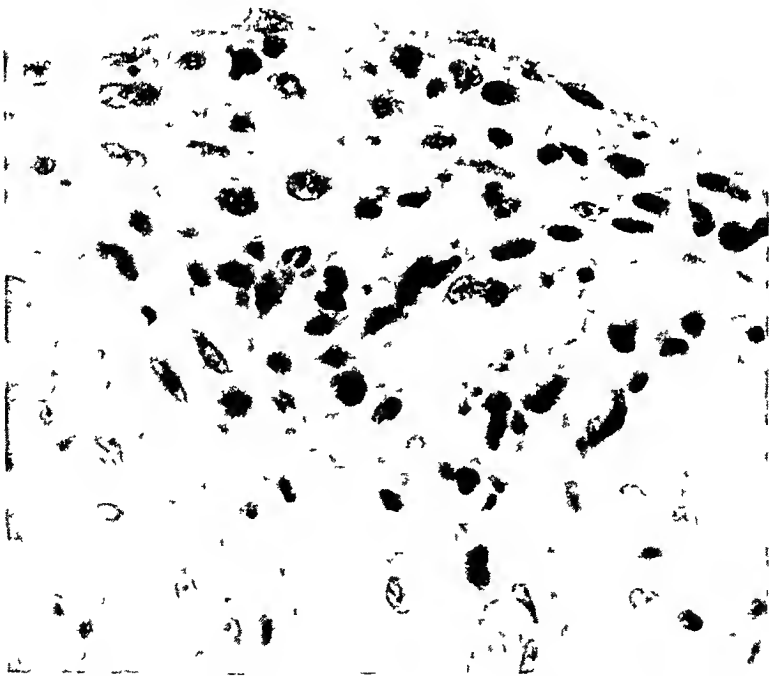


Fig 3 (rabbit 299) —High power magnification of subendocardial focus exhibited in figure 2, showing cell types in greater detail, which include enlarged spindle-shaped reticulum cells, similar, but more rounded, large mononuclear cells, smaller round cells resembling plasma cells, and lymphocytes, as well as a few mononuclear eosinophils and polymorphonuclear neutrophils and eosinophils. Attention is called to the similarity of this reaction to that seen in rheumatic fever. Magnification, $\times 930$

cells accompanied the interstitial reaction. Detail of such a proliferative focus beneath the endocardium is shown in figure 3. The actual degenerative changes in the heart muscle were less easy to follow. However, occasional muscle fibers exhibited a frankly necrotic hyalinized cytoplasm (fig 4). Other irregular hyalinized remnants were seen which presumably were portions of necrotic muscle fibers.

Another evidence of myocardial damage was seen in the distinct hypertrophy in all of the muscle fibers. This hypertrophy was evident, both in the increased amount of cytoplasm and in the altered nuclear characters, and was readily seen when such a section was compared

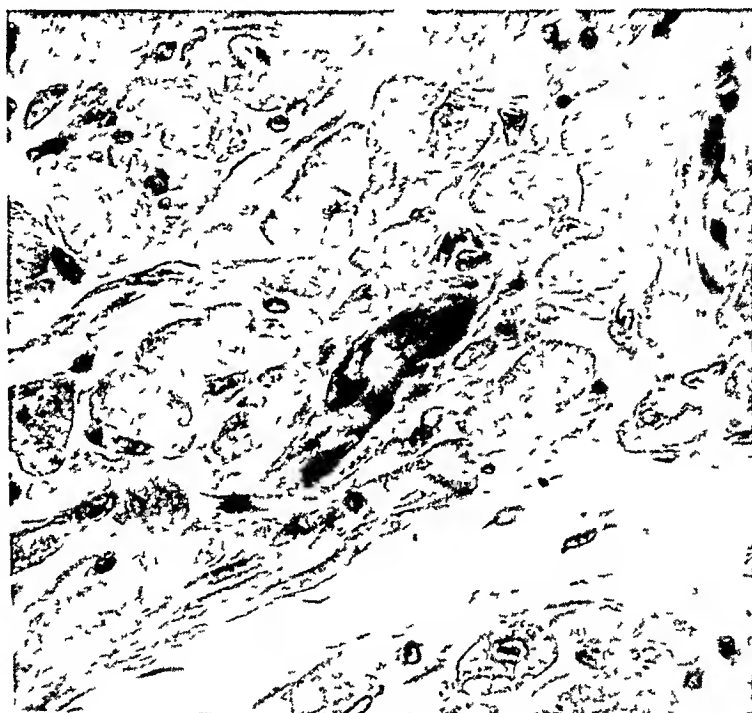


Fig 4 (rabbit 299)—One of many frankly necrotic, hyalinized muscle fibers and showing early proliferative reaction of the surrounding interstitial or reticular cells. Note the increased size of the surrounding muscle fibers and the alteration in nuclear characters considered evidence of cell injury. Magnification, $\times 930$.

with that of a normal animal. As this cell and nuclear enlargement was apparent after seventy-two hours, it was probably a swelling, preceding or indicating degeneration, rather than a compensatory hypertrophy. Rabbit 300, treated like rabbit 299, showed a less striking, but comparable, histologic change.

Rabbit 305, receiving the sublethal dose of 10 mg per kilogram and killed eleven days later, revealed an equally interesting microscopic picture in the heart muscle (fig 5). In foci, particularly in the zone beneath the endocardium, the interstitial tissue appeared more prominent

than usual, owing both to degeneration and disappearance of muscle fibers and to a proliferation of the supportive reticulum cells in response to injured and necrotic muscle. Where the reaction was most apparent, bits of degenerating or frankly necrotic hyalinized muscle were usually seen. In one small focus of proliferation, the cells had the cytologic characters of polyblasts. A more chronic type of reaction was seen in rabbit 308. This animal received three doses of 5 mg. per kilogram at four day intervals and died ten days after the last dose. The heart muscle showed small relatively dense but cellular foci of fibrosis centered about atrophic and coagulated muscle fibers. This appearance of com-

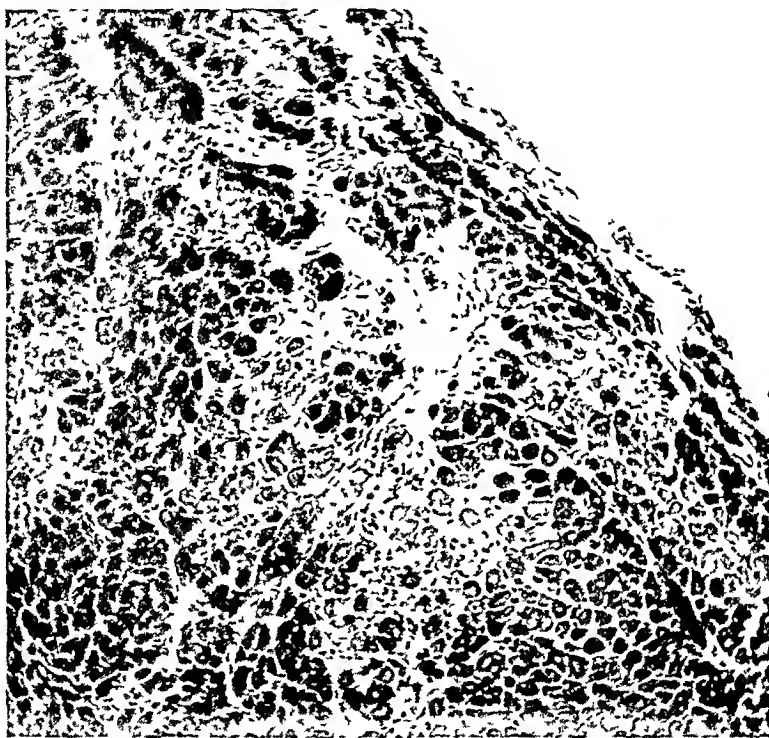


Fig. 5 (rabbit 305) —Photomicrograph showing rarefaction of the heart muscle, numerous foci of interstitial proliferation and enlargement of the muscle cells. Magnification, $\times 175$.

plete or incomplete coagulation was noted in many of the fibers throughout the section. Further evidence of injury was the vacuolation occurring in the cytoplasm of numerous muscle cells. The focal interstitial cytologic response to the injured muscle, as it occurred in rabbit 299 and rabbit 305 in particular, recalled that of the Aschoff reaction of acute rheumatic fever. Figures 2 and 3 showing an accumulation of large mononuclear cells with accompanying lymphocytes and plasma cells in the subendocardial nodule illustrate the similarity of the reactions.

Although we were primarily concerned with the pathologic alteration in the heart muscle, we examined sections of other viscera and tissues

exclusive of the nervous system in the majority of the animals. Rabbit 308 showed necrosis of numerous fibers in a section of skeletal muscle. Other sections of skeletal muscle studied did not reveal a distinctive lesion. The impression gained in preliminary examinations that a widespread degeneration of skeletal muscle of the diaphragm and of the smooth muscle in the small intestine had occurred¹² was probably premature. A more extensive study of these tissues would be necessary to determine this. Lesions comparable in severity to those in the heart muscle were not apparent on examination of liver, kidneys, spleen or adrenal glands. The heart muscle in this study bore the burden of the toxic effect of emetine.

SUMMARY

Lethal or sublethal doses of emetine hydrochloride in rabbits caused severe injury to the heart muscle. An interval of time was required for morphologic changes to become apparent. Animals dying in less than forty-eight hours showed evidence of heart failure in an interstitial edema of the heart muscle, indicated by spreading apart of individual fibers. In animals surviving lethal or sublethal doses for three or more days, necrosis of some fibers and a degenerative swelling in the remaining muscle fibers became evident. This resulted in a rarefaction of the heart muscle and in focal proliferations of the interstitial tissue in response to the necrotic muscle fibers. Hypertrophied reticular cells were apparently transformed into large mononuclear cells. Lymphocytes and plasma cells, as well as eosinophils and polymorphonuclear neutrophils, were found in such foci. Remaining muscle fibers increased in size, and the nuclei showed changes in size and distribution of chromatin interpreted as evidence of injury. A more chronic intoxication produced with divided lethal doses of emetine hydrochloride resulted in small cellular scars in the myocardium centered about necrotic muscle fibers. One animal showed necrosis of skeletal muscle fibers, and another focal necrosis in the liver, but no lesions of consistent occurrence were observed that were comparable in severity to that in the heart muscle. In this study, the lesions observed in the heart muscle of animals dying or put to death seventy-two or more hours after lethal or sublethal doses of emetine administered by mouth were considered sufficient to cause the death of the animals. Attention was called to the similarity of the Aschoff reaction of acute rheumatic fever and this effect of emetine.

CHLOROFORM IN THE BRAIN, LUNGS AND LIVER

QUANTITATIVE RECOVERY AND DETERMINATION

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A search of the literature on deaths due to chloroform impresses one with the extremely meager and inconsistent reports on the quantity of chloroform found in the organs of cadavers.

Fischer¹ in a case of complete narcosis, found 55 mg. in 780 Gm. of lungs and blood, 70 mg. in 480 Gm. of brain, a trace in 445 Gm. of liver, kidney and spleen. Sedya,² in a case of beginning narcosis found 4 mg. in the brain, 72 mg. in 1,000 Gm. of stomach and contents, 2 mg. in liver, kidney and spleen, 42 mg. in lungs, heart and blood. Tissot³ found 450 mg. in 1,500 Gm. of brain, 350 mg. in 1,500 Gm. of liver, 0.023 per cent in muscle (230 mg. in 1,000 Gm.). Nicloux⁴ found 0.0555 per cent in brain (555 mg. in 1,000 Gm.), 0.05 per cent in liver, 0.046 per cent in kidney, 0.038 per cent in spleen, 0.021 per cent in muscle, 0.07 per cent in arterial blood, 0.04 per cent in heart, 0.083 per cent in spinal cord. It is needless to give results of other workers in this field, such as Grehant and Quinquand,⁵ Luedeking,⁶ Pohl,⁷ Angiolani,⁸ Buckmaster and Gardner,⁹ because their results show similar deviations.

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From the chemical laboratories of the Chief Medical Examiner's Office of New York City, and of Washington Square College, New York University.

1 Fischer. *Jahresb. d. chem. Untersuchungsamtes d. Stadt Breslau*, f. d. Zeit April 1, 1894—March 31, 1895.

2 Sedya. *Lesser Vierteljahrsschr. f. gerichtl. Med.*, 1899.

3 Tissot. *J. de physiol. et de path. gen.* **8**, 423, 1906.

4 Nicloux, M. *Compt. rend. Soc. de biol.* **60**, 248, 1906.

5 Grehant, N., and Quinquand, C. E. *Compt. rend. Acad. d. sc.* **97**, 753, 1883.

6 Luedeking, C. *Am. Chem. J.* **8**, 358, 1886.

7 Pohl, T. *Arch. f. exper. Path. u. Pharmacol.* **28**, 239, 1890-1891.

8 Angiolani, P. *Chem. Zentralbl.* **62**, 1068, 1891.

9 Buckmaster, G. A., and Gardner, J. A. *Proc. Roy. Soc., London, Series B* **78**, 414, 1906, **79**, 309, 1907.

The methods used by workers in this field for the quantitative determination of chloroform in tissues were those suggested by Schmiedeberg,¹⁰ Ludwig and Fischer,¹¹ Nicloux,¹² Gibson and Laird-law,¹³ Buckmaster and Gardner⁹ and others. The procedures involved in these methods are, first, the isolation of the chloroform by steam distillation or plain distillation or by passing a neutral gas, such as carbon dioxide or nitrogen, through the mixture, second, the conversion of the chlorine in the chloroform to an ionizable chloride, third, the determination of this chloride by the usual gravimetric or volumetric procedures. These methods are extremely laborious, and analyses made by means of them have proved to us that the results obtained are unreliable. The explanation for this may lie in the fact that small quantities are always involved (from 0.005 to 0.080 Gm of chloroform) and the conversion of chloroform to chloride ions is not quantitative.

In 1914, Fujiwara¹⁴ described the pyridine color reaction with chloroform and related substances (sensitivity 1:1,000,000). He also attempted to use this reaction for estimating chloroform in body fluids and tissues. In 1926, Cole¹⁵ described a colorimetric method for the quantitative determination of chloroform based on the Fujiwara reaction. This method was tried out and critically studied in the present work and found to be fairly accurate. Certain modifications, however, were tried and found to improve the method, namely:

1. We advise using 5 cc of distillate for the colorimetric determination instead of 1 cc. Since the total distillate is 250 cc, the actual value found in 5 cc is multiplied by 50 and not by 250, as is the case when 1 cc of distillate is used. This makes the method more accurate.

2. After the color has developed, there are present two layers, the upper pyridine layer contains the developed pink color. Cole pipets this off into a colorimeter cup. The disagreeable, poisonous vapor of the pyridine makes this objectionable. It was found that if exactly 20 cc of water is added and mixed, the two layers merge into one, the entire mixture taking on the pink color, no turbidity, even in weak chloroform solutions, is then encountered. This modification reduces the sensitivity to 1:100,000, which is quite adequate for most toxicologic work.

3. Colored glass disks were devised to be used as permanent standards in the Hellige-Klett colorimeter (comparative type).

10 Schmiedeberg. Inaug. Diss., Dorpat, 1866.

11 Ludwig and Fischer, in Autenrieth and Warren, *The Detection of Poisons*, Philadelphia, P. Blakiston's Son & Company, 1921, p. 38.

12 Nicloux, M. *Compt. rend. Soc. de biol.* **60**, 88, 1906, **63**, 391, 1907, **91**, 1282, 1924.

13 Gibson, C. S., and Laird-law, P. P. *Guv's Hosp. Rep.* **62**, 359, 1922.

14 Fujiwara, K. *Sitzungsber. u. Abhandl. naturforsch. Gesellsch. Rastock* **6**, 1, 1914.

15 Cole, W. H. *J. Biol. Chem.* **71**, 173, 1926.

With these modifications, the method used in this work is in detail as follows

THE METHOD

Isolation of Chloroform from Tissues—The brain, lungs and liver, as soon as removed from the body, are placed in a clean jar, sealed an tight, and placed in the refrigerator. When the material is ice cold, about 150 Gm of the tissue to be examined is ground up. From this minced material, 100 Gm is weighed out and quickly placed in a 500 cc distillation flask, about 100 cc of water is added, also a little tartaric acid—enough to make the mixture acid in reaction. The material is then subjected to steam distillation, a long, well cooled condenser and an adapter being used. The receptacle for collecting the distillate, a 300 cc Erlenmeyer flask, should contain about 10 cc of ice cold, acidified (HCl) water and should be packed in ice. The tip of the adapter should reach into this ice cold water contained in the distillate receptacle. With these precautions there should be no loss of chloroform during distillation. Experiments have proved that if 250 cc of distillate is collected, all of the chloroform originally present in the tissue will have passed into the distillate. The distillate is well mixed, measured, stoppered and kept cold. For the colorimetric determination, 5 cc portions of the distillate are taken.

Preparation of Standards for Use in Colorimetric Estimation of Chloroform in Distillate—R-C-halogen compounds, such as bromoform, chloroform, chloral and iodoform, also give the Fujiwara color reaction. It is therefore essential at the outset to determine whether chloroform or some other one of the aforementioned group is present. We are now engaged in the standardization of a method for the determination of the foregoing series of compounds in human tissues.

The materials necessary for the colorimetric determination of chloroform in tissues are chemically pure pyridine (colorless), 20 per cent sodium hydroxide solution and standards such as are described in the following paragraphs.

The chloroform standards are made as follows. One gram of pure chloroform is weighed out. This is best done by placing a little more than 1 Gm of chloroform in a weighing bottle having a ground glass stopper. The chloroform is allowed to evaporate spontaneously, being weighed from time to time (with weighing bottle stoppered) until the weight of chloroform in the bottle is just 1 Gm. This gram of chloroform is then dissolved in about 900 cc of water contained in a 1 liter volumetric flask, 5 cc of hydrochloric acid is added and, finally, enough water is added to bring the total volume to exactly 1 liter, the whole is then thoroughly mixed. Precautions must be taken to avoid evaporation of the chloroform during the transfer. The solution contains 1 mg of chloroform in 1 cc. From this stock solution a series of weaker standards are made having the following chloroform values: 0.5, 0.1, 0.01, 0.005, and 0.0025 mg, respectively, in 1 cc. These standards, even if kept in the refrigerator, are good for only one week.

Permanent colored glass standards (an alternate standard) are prepared as follows. A series of glasses with varying depths of orange-pink color, simulating the different depths of colors obtained by various concentrations of chloroform when subjected to the pyridine test, are selected. Small disks of these glasses are cut and fitted into the circular openings of the wheel of the Hellige-Klett colorimeter, comparative type (figs 1 and 2). These colored disks are then standardized by chloroform solutions of known concentrations. The color disks 1 to 8, respectively, have the following values: Chloroform in 5 cc of solution, 0.125 mg, 0.25 mg, 0.375 mg, 0.5 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg. These colored glass standards keep indefinitely if kept in the dark.

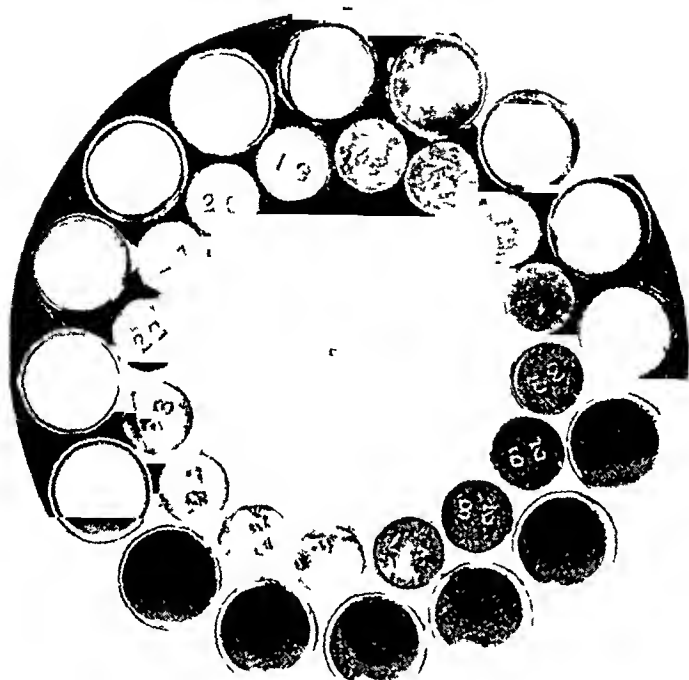


Fig 1—Wheel holding standardized colored glass disks used with the colorimeter



Fig 2—A Hellige-Klett colorimeter of the comparative type (made by the Klett Manufacturing Company New York)

Colorimetric Estimation of Chloroform in Distillate—The colorimetric method, using the chloroform standards, is applied as follows. Into five clean, dry, 50 cc test tubes (Folin digestion tubes may be used), 5 cc portions of the five standards containing, respectively, 0.5 mg, 0.1 mg, 0.01 mg, 0.005 mg and 0.0025 mg of chloroform in 1 cc are measured. Into a similar test tube, 5 cc of the distillate is pipetted. To each of the tubes is added 5 cc of chemically pure (colorless) pyridine, and then 10 cc of 20 per cent sodium hydroxide, the contents of the tubes are mixed thoroughly, the tubes are corked loosely to avoid evaporation. Then the tubes are placed in a boiling water bath for exactly one minute and then cooled quickly with running water. Now exactly 20 cc of water is added to each tube and mixed. The color of the unknown is compared with the colors of the five standards. Should the unknown match the color of the standard containing 0.01 mg in 1 cc (0.05 mg in 5 cc), the chloroform content of the entire distillate (250 cc) would be 50 times 0.05 mg, or 2.5 mg. Since 100 Gm of tissue was used in getting the distillate and the recovery is 92 per cent (see under heading "Percentage of Recovery"), there are 2.5 times 1.087, or 2.72 mg of chloroform in the 100 Gm used for analysis. If none of the five standards exactly matches the color of the unknown, the latter is compared in a colorimeter with that one of the five standards which has a color depth closest to the unknown. From the readings on the colorimeter, the chloroform content in 100 Gm of tissue is calculated as follows:

$$\frac{\text{Standard}}{\text{Unknown}} \times \frac{\text{Value of standard used in}}{\text{mg of chloroform}} \times \frac{250}{5} \times 1.087 \left\{ \begin{array}{l} \text{correction for per-} \\ \text{centage of recovery} \end{array} \right\} = \text{mg chloroform in 100 Gm tissue}$$

The colorimetric method, using colored glass standards, is especially adapted where routine determinations of chloroform are being done over long periods. The standard glasses are permanent. This method eliminates the preparation of a series of chloroform standards for each and every chloroform determination. It is applied as follows. Into a clean, dry test tube 5 cc of the distillate is pipetted, 5 cc of chemically pure (colorless) pyridine is added and then 10 cc of 20 per cent sodium hydroxide, the contents of the test tube are then mixed, the test tube is corked loosely to avoid evaporation. The tube is placed in a boiling water bath for exactly one minute and then cooled quickly in running water. Now exactly 20 cc of water is added and mixed. This colored solution is placed in the cell of the Hellge-Klett colorimeter. Then the wheel of the instrument is turned, the color of each disk being compared with that of the solution in the cell. The disk that exactly matches the color of the solution in the cell is noted. The value of this disk in terms of milligrams of chloroform is known (see previous paragraph on permanent colored glass standards).

Calculation

$$\frac{\text{Value of colored disk in mg chloroform}}{\text{mg chloroform}} \times \frac{250}{5} \times 1.087 \left\{ \begin{array}{l} \text{correction for} \\ \text{percentage of} \\ \text{recovery} \end{array} \right\} = \text{mg chloroform in 100 Gm tissue}$$

Percentage of Recovery—Control Experiments—Several series of control experiments were carried out. 5 cc, 10 cc, 20 cc and 40 cc of the standard 0.1 per cent chloroform solution (equivalent to 5 mg, 10 mg, 20 mg and 40 mg of chloroform) were added and intimately mixed with a series of 100 Gm portions of ice cold, ground-up brain material. The method of isolation and colorimetric determination

described was then resorted to. The recovery was not complete. It ranged between 90 per cent and 94 per cent, the great majority of determinations giving a 92 per cent recovery. Still, this 92 per cent recovery was so constant in all our determinations that we feel that the method is satisfactory and reliable.

Effect of Putrefaction on Chloroform Recovery—In a series of experiments it was found that the chloroform content of tissues decreases with standing, especially if these are not kept in the refrigerator. The order of recovery of chloroform from the tissues on standing was: one day, 82 per cent, three days, 65 per cent, six days, 49 per cent, ten days, 31 per cent, forty-two days, 18 per cent.

Estimations of the Chloroform Content of Tissues by the Colorimetric Method

Case	History	Chloroform Content of Tissues, Mg per 1,000 Gm		
		Brain	Lungs	Liver
1	Suicide	432	395	238
2	Suicide	480	462	275
3	Suicide	410	425	218
4	Suicide	390	355	205
5	Homicide	372	485	192
6	Suicide	384	405	194
7	Suicide	374	394	190
8	Abortion, shock	162	115	74
9*	Abortion, hemorrhage	60	22	28
10	Tonsil operation, shock	136	105	72
11	Minor operation, shock	135	95	75
12	Minor operation, shock	145	98	78
13	Minor operation, shock	120	106	68
14	Minor operation, shock	122	92	65
15	Abortion, shock	182	145	88
16†	Minor operation, shock	70	120	24

* Anesthesia was stopped, and the patient was beginning to recover.

† The patient died while anesthesia was being administered.

Much of the decomposition of the chloroform is due to the fact that the putrefying tissue gets increasingly alkaline. The chloroform does not decompose so rapidly in an acid medium. The curves we obtained are not regular. Many factors are evidently involved. We are still investigating this phase of the subject.

RECOVERY OF CHLOROFORM FROM THE BRAIN, LUNGS AND LIVER
OF PERSONS WHO DIED FROM OR WHO AT THE TIME OF
DEATH WERE UNDER THE INFLUENCE OF CHLOROFORM

By means of the method just described, the brain, lungs and liver in a series of cases of death in which chloroform was involved were analyzed. The results are shown in the accompanying table.

In cases 1 to 7 death was due solely to chloroform, administered in excessive amounts. In these cases, the brain contained between 372

and 480 mg of chloroform in 1,000 Gm of tissue. The lungs contained between 355 and 485 mg in 1,000 Gm of tissue. The values in the brain and in the lungs ran parallel. In four of the seven cases, the lungs showed slightly higher values. The chloroform content of the liver ranged between 190 mg and 275 mg in 1,000 Gm of tissue. The chloroform content of the liver was only about 58 per cent of the chloroform content of the brain.

In cases 8 to 16, death was due to shock. Chloroform was administered by a physician using the care and the technique necessary in chloroform anesthesia. The chloroform content of the brain ranged between 120 mg and 182 mg in 1,000 Gm of tissue. In case 9, the value found was only 60 mg. The reason for this was that anesthesia had been stopped, and the patient was beginning to recover. Death was due to hemorrhage. In case 16, the chloroform content was only 70 mg owing to the fact that the patient died of shock during the beginning of anesthesia.

The chloroform content of the lungs in cases 8 to 16 was less than that of the brain (ranging from 95 to 145 mg) owing to the fact that the patients had been fully anesthetized and the administration of chloroform therefore had been partially or entirely stopped. For a short time during the initial administration of chloroform the lungs contained more chloroform than the brain, as evidenced by case 16, in which the patient died during this period.

The liver in these cases also contained less chloroform than the brain.

SUMMARY

When chloroform-containing distillate is treated with pyridine and sodium hydroxide and heated in the water bath for one minute a pink color develops. The color produced is read against similarly treated standard chloroform solutions. The use of permanent colored glass standards for the colorimetric work is described.

After death the chloroform content of the tissues decreases daily. After forty-two days, only 18 per cent of the original amount present is recoverable. The chloroform content of the brain, lungs and liver in seven cases of death due to excessive administration of chloroform was as follows: brain, from 372 to 480 mg, lungs from 355 to 485 mg and liver, from 190 to 275 mg in 1,000 Gm.

The chloroform content of the brain, lungs and liver of nine patients after chloroform anesthesia, given in preparation for surgical operation, was as follows: brain from 120 to 182 mg, lungs, from 92 to 145 mg, and liver from 65 to 88 mg, in 1,000 Gm.

THE KIDNEYS IN YELLOW FEVER *

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The existence of renal changes during an attack of yellow fever was noted by the earliest observers. Today it is known that these changes are characterized by their constancy and their relationship to the high fatality of yellow fever. Appearing among the first symptoms of the disease, they become intensified as it develops, in many fatal cases there is total suppression of renal function prior to death.

Recent clinical observations have shown how important a part renal disturbances play in yellow fever. Beeuwkes¹ noted these disturbances in all the clinical cases which he observed in West Africa. Fraga,² referring to recent cases in Rio de Janeiro, said that the renal lesions were usually severe and constant. Lins,³ who studied a great number of patients in the Hospital of São Sebastião, Rio de Janeiro during the epidemic of 1928, found that renal lesions were present in all cases. Of the four clinical forms of yellow fever described by Lins,⁴ one is exclusively renal and the remaining three are of the hepatorenal type, differing from each other only in the degree of intensity of the damage.

The pathologic anatomy of the kidneys in yellow fever is, then, a matter of great interest. The present paper presents my recent observations in this field under the supervision of Professor Oskar Klotz.

MATERIALS USED

Material from eighty-seven patients with yellow fever and from thirty-four monkeys (*Macacus rhesus*) experimentally infected with yellow fever was used. Of the cases in man fifty-three occurred in West Africa and thirty-four in South

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The studies and observations on which this paper is based were conducted in the Department of Pathology of the University of Toronto, Canada, with the support and under the auspices of the International Health Division of the Rockefeller Foundation.

1 Beeuwkes, H. Report on Epidemic of West African Yellow Fever on the Gold Coast in 1926. International Health Division, Rockefeller Foundation (unpublished).

2 Fraga, Clementino. The Yellow Fever Epidemic at Rio de Janeiro, Pub. Health Rep. **43** 3079, 1928.

3 Lins, S. A. Contribuição ao estudo clínico de febra amarela, Arch. de hyg. **3** 193, 1929.

America, all the experimental animals had been infected with West African virus. This material was part of the excellent collection assembled by Professor Klotz.

The stains used were hematoxylin and eosin tetra-brom-di-chlorfluorescein and methylene blue (methvithionine chloride, U S P) and silver nitrate. Perl's and Goodpasture's methods were also employed. The material was for the most part fixed in solution of formaldehyde, but in a small number of cases Zenker's solution was used.

RENAL LESIONS IN YELLOW FEVER IN MAN

Since Councilman's⁴ description in 1890, all writers have been more or less in agreement as to the occurrence of the following lesions of the kidneys in yellow fever: (a) cloudy swelling, fatty degeneration, hyaline and granular degeneration of the cells of the convoluted tubules, (b) necrosis, (c) presence of granular debris with hyaline, granular and calcareous casts within the tubules, (d) congestion and hemorrhage, (e) congestion of the glomerular vessels, (f) dilatation of the capsular space with the occasional presence of granular or hyaline material from hemorrhage and from necrosis and desquamation of the epithelial cells of Bowman's capsule. My observations on these changes are as follows:

Degeneration—Degeneration was most frequently localized in the epithelium of the convoluted tubules of the first and second order and in Henle's loops. It presented variations that ranged from a simple swelling to complete hyaline and granular disintegration. The swelling of the epithelial cells was present in all the cases, and the majority of tubules were affected. The tubules were often considerably dilated but some were completely occluded by the swollen and desquamated cells.

The hyaline and granular degeneration was constant and involved the majority of the convoluted tubules. The cell protoplasm showed an increased density, was irregularly stained, and was divided into multiple globules, unequal in size and color. The nuclei were at times pyknotic, at other times karyolytic. In every case the customary pseudocilia were as Councilman⁴ had noted, markedly exaggerated along the free border of the cells.

Fatty degeneration was also constant, and was recognized by the presence in paraffin sections, of characteristic vacuoles in the cytoplasm. In thirty-nine cases, in which material was stained with sudan III, the presence of fat was noted. These fat granules were almost always localized in the bases of the cells and were always irregularly dis-

⁴ Councilman W T. Extract from the Report on the Etiology and Prevention of Yellow Fever, by George H. Sternberg. U S Marine Hospital Service, 1890, pp 151-159.

tributed in the convoluted tubules, in Henle's loops and often in the collecting tubules. In the great majority of cases, the fat was present in small quantities, sparing a great number of tubules and many individual cells in the same tubule. In two or three cases there was practically no fat, and in eight fat was present in great quantities, appearing in large masses in the majority of the tubules. Occasionally I was able to discern small fatty granules in the glomerular tufts or in the cells lining Bowman's capsule.

Necrosis—In all the cases necrotic cells were observed, but in most instances such cells were few. In the great majority of cases they were distributed irregularly in the convoluted tubules and at times a few were seen elsewhere. In only five cases did I find extensive and widely distributed tubular necrosis.

Casts—Granular material or debris in irregular masses, occupying in almost every instance the lumina of the convoluted tubules, was constantly observed. Sometimes the debris formed a large agglomerate mass completely filling the lumen of a tubule, but ordinarily the amount was small and of irregular form.

Hyaline and granular casts were also present but generally in small number and found in the lumina of the convoluted and the collecting tubules. The hyaline casts were homogeneous and frequently showed marked variation in the depth of the stain. Many contained vacuoles. Some of them had two distinct parts, a homogeneous center and a very finely granular envelope.

In most cases the calcareous casts appeared to be localized in the interior of Henle's loops and in the convoluted tubules, with an occasional one in the collecting tubules. They were seen as very small and agglomerated granules or, at times, as more or less globular masses, some showing very fine striations radiating from the center toward the periphery. These casts were not present in all the cases, but were noted in about 60 per cent of them, ordinarily occupying the lumina of two or three tubes in each section.

The fact that iron had frequently been observed in the calcareous deposits in various pathologic conditions of the kidneys (Klotz,⁵ MacCallum⁶) led me to search for this substance in the tissue under study. For this purpose sections from ten of the kidneys in which such casts

5 Klotz, Oskar. Yellow Fever in West Africa, De Lamar Lectures, Baltimore, Williams & Wilkins Company, 1927-1928, p. 22.

6 MacCallum, W. G. Textbook of Pathology, ed. 4, Philadelphia, W. B. Saunders Company, 1928.

had been seen in great numbers were stained by Peil's method in one series and with silver nitrate in another. By these methods the reaction for iron was easily obtained.

Congestion and Hemorrhage—In all cases congestion was noted, indicated by the dilatation and engorgement of the small vessels. In the great majority of cases congestion appeared to be much more severe in the medullary zone than in the cortical zone, which may perhaps be explained by the compression of the small vessels in the cortical zone due to the swelling of the convoluted tubules. The severity of the congestion was variable but it was present to some degree in all.

I did not observe definite hemorrhage in any case, but in the instances in which congestion was most severe, a few blood corpuscles were found outside the vessels.

Glomerular Changes—Slight dilatation of the glomerular capillaries was of constant occurrence, and did not appear to vary in intensity. The capsular space which was always more or less dilated was empty in the majority of cases. Necrosis and desquamation of the cells covering Bowman's capsule were more or less frequent. Occasionally the capsular space contained granular material, and in one instance a colloid-like substance. In no case did I observe rupture of Bowman's capsule and only in those cases in which congestion was very intense did I find blood in the capsular space.

RENAL CHANGES IN THE EXPERIMENTAL ANIMALS

All the renal lesions usually found in cases in man were encountered in the experimental material, and the degree of involvement was essentially the same.

Cloudy swelling was present in all cases, affecting a great number of tubules. Moderately dilated tubules were only rarely observed, and then in small numbers. In the cases of more extensive swelling the lumina of the tubules were obliterated by the swollen cells.

Hyaline and granular degeneration was found in a small number of tubules, and the nuclei of the degenerated cells were generally pyknotic.

Fatty degeneration, which was also present in all the cases, appeared in the same irregularity as in cases in man, varying with the extent and intensity of the other degenerative changes. In twenty-five of the cases sections were stained for fat, and in fifteen of these a few small droplets were found at the bases of the cells in a few convoluted and collecting tubules. In eight cases the fatty change was extreme, involving

all cortical tubules and some of those in the medullary zone, whereas in two other cases fat was almost entirely absent

I saw small numbers of necrotic cells in the majority of the cases always irregularly scattered through the various tubular structures of the kidney. In a few cases necrosis was extensive

Granular debris, forming sometimes hyaline, granular and calcareous casts, was also commonly observed, but in relatively small quantity. Casts were entirely absent in many cases. On careful search calcareous deposits were demonstrated in only about 30 per cent of the cases. In these they presented the same appearance as in the cases in man and were also found to contain iron

Congestion was regularly present, but always in moderate degree and more marked in the medullary than in the cortical zone. The glomeruli only rarely showed engorgement. The capsular space was moderately dilated in most cases, and only in two instances did it contain any debris. In a few cases Bowman's capsule showed necrosis and desquamation of the lining cells

NUCLEAR CHANGES

In the human cases, as in the experimental, the nuclear changes presented a curious appearance not hitherto described. All phases of degeneration—pyknosis, karyorrhexis and karyolysis—were observed in the cells undergoing hyaline and granular degeneration. In the cases in man, karyolysis occurred more frequently, with prominent chromatin granules in the interior of the nuclei. Often the central chromatin filaments had disappeared, leaving the nucleus pale. In the experimental cases, in which the changes were, in general, less pronounced, the condensed and deeply stained chromatin was more frequently observed

In five of the cases in man, all African in origin I found in the center of some of the degenerated nuclei homogeneous globular masses surrounded by a clear zone. These masses were generally irregularly ovoid or irregularly spherical. They varied in size from about one-third that of the nucleus to approximately its full dimensions. These intranuclear structures or bodies were rose-colored in the hematoxylin and eosin preparations and an intense and brilliant red in sections stained with tetra-brom-di-chloro fluorescein and methylene blue, there was never more than one in each nucleus. The chromatin in these nuclei appeared to adhere to the nuclear membrane, forming irregular layers, but at times it was entirely absent, and the inclusion body was the only structure contained within the nuclear membrane. Only once did I observe distinctly a nucleolus in these nuclei. It was stained pale blue and was



Fig 1—Nucleus of a cell of a convoluted tube, showing an inclusion in its interior



Fig 2—Nuclei of three cells showing inclusions



Fig 3—Nucleus containing an inclusion with irregular and smooth borders (less frequent form), the nucleolus being very clearly seen. This illustration and that in figure 4 are taken from colored sketches (laminae stained with tetra-brom-di-chlorfluorescein and methylene blue)

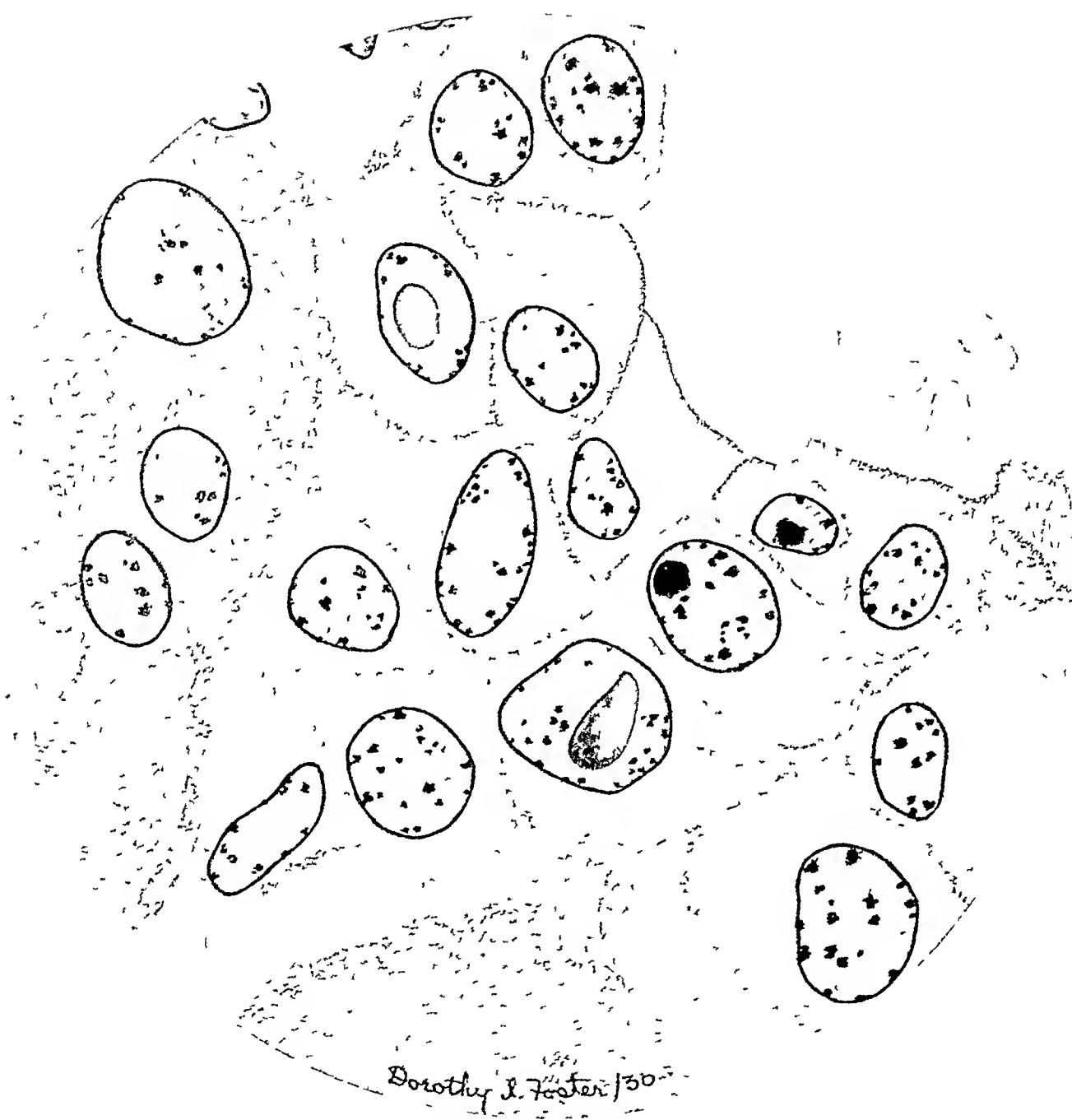


Fig 4—Inclusions of oval form with convex borders (common type), occupying the nuclei of two cells

entirely isolated from the nuclear mass. In one case the inclusion bodies were relatively numerous and were found within several cells of the same tubule, but in other cases they were scarce and a prolonged search was necessary in order to locate one or more of them.

The presence of similar bodies was also noted in the infected monkeys, but less regularly. In the cases in man the bodies were found in every instance in which Zenker's solution had been used as a fixative for the material, but in cases in monkeys, they were found in only four of the fifteen cases in which the material had been fixed in this solution.

Results of Examination of Kidney Tissue from Fifteen Autopsies for Intracellular Acidophil Bodies

Autopsy	Clinical Diagnosis	Renal Lesion	Acidophil Masses
A 5 30	Infantile asthenia	None	Absent
A 9 30	Syphilitic aortitis and stenosis of the coronary arteries	Nephrosis	Present
A 11 30	Chronic pulmonary tuberculosis	None	Absent
A 16 30	Carcinoma of the thyroid gland	Chronic interstitial nephrosis	Absent
A 18 30	Otitis media and meningitis	None	Absent
A 22 30	Generalized arteriosclerosis	Pyelonephrosis	Absent
A 23 30	Acute gangrenous stomatitis	Chronic nephrosis and hyaline degeneration	Present
A 24 30	Septic endometritis	None	Absent
A 25 30	Tumor of the brain with hydrocephalus	None	Absent
A 26 30	Asphyxia	None	Absent
A 27 30	Acute pyelonephritis	Pyelonephrosis	Absent
A 29 30	Bulbar paralysis	Nephrosis	Present
A 32 30	Arteriosclerosis	Chronic nephrosis	Absent
A 34 30	Congenital bladder trouble	Pyelonephrosis	Absent
A 36 30	Carcinoma of the pancreas	Nephrosis	Absent

In order to determine whether these acidophil bodies could be found in cases other than those of yellow fever, I collected kidney tissue from fifteen autopsies on human beings. This material was fixed in Zenker's solution and stained with hematoxylin and eosin in one series and with tetra-brom-di-chlorfluorescein and methylene blue in another. The table gives the observations. In three cases the kidney showed intracellular, more or less homogeneous, acidophil masses, of irregularly spherical form and with smooth borders, similar to those encountered less frequently in the cases of yellow fever. I did not observe the irregularly ovoid masses with convex borders which were frequently seen in cases of yellow fever. All of these masses failed to take Goodpasture's stain, appearing only slightly dark and showing the presence of colloid material, while in the same preparations the nucleoli were bright red and the chromatin bluish violet.

In all the stained material which was fixed in Zenker's solution, in the human, as well as in the experimental, cases of yellow fever, I fre-

quently observed nuclei that were slightly increased in size and contained irregularly agglomerated granules, some of which were blue and some rose-colored

One of the cases in man showed numerous degenerated cells in the convoluted tubes. Some of these contained compact, homogeneous nuclei, apparently solidified and intensely red, some were filled with fine red granules contained in a pale rose-colored hyaline mass, which completely filled the interior, some showed less intensely colored granules, which had lost their contours and become fused with the mass of protoplasm. These various pictures gave the impression of phases of a nuclear degeneration in which the nucleus is at first homogeneous and compact and by degrees breaks up into innumerable granules until it becomes fused with the protoplasm in granular or hyaline degeneration. I succeeded in demonstrating nuclei of similar character in only two other cases in man and in one of the experimental cases.

COMMENT

Councilman,⁴ in 1890 in describing the pathologic changes in the kidneys in yellow fever, drew attention to the intensity of the degenerative processes localized in the cells of the convoluted tubules and pointed out, as the principal lesion the hyaline and granular degeneration of these same cells, in which the cytoplasm is described as being composed of immense numbers of hyaline granules, stained deeply with eosin. He noted also fat vacuoles in the protoplasm of these cells, and dilated convoluted tubules filled with granular hyaline debris. He even distinguished the glomerular changes through the dilatation of the capsular space and the presence, in its interior of granular material and frequently of round hyaline masses. He noted the presence in many cases of a colloid material and of crystals in the lumina of the tubules. He described the colloid material as being composed of round, and at times irregular, masses which often combined to form long chains. The material of these structures was entirely hyaline and composed of numerous layers, like a grain of starch. He described the crystalline masses that he found in all cases as having a yellow or greenish-yellow color, neat and sharpened borders and numerous lines or cracks which radiated from the center toward the periphery. He noted that these crystals did not take the stain of any of the reagents used. He also found epithelial casts and observed leukocytes within the tubules. Marchoux and Simond,⁷ in their obser-

⁷ Marchoux E, and Simond P-L. *Études sur la fièvre jaune*. Quatrième mémoire de la mission française à Rio de Janeiro, Ann de l'Inst Pasteur **20** 161, 1906.

vations in 1906 reported the presence of fatty degeneration, which was extensive in some cases and slight in others. The first was observed especially in cases terminating in anuria. They also reported the presence of casts composed of desquamated cells and of extravasated red cells at times obliterating the lumina of several tubes. Elliott⁸ in 1918, referring to cases in Guayaquil, described changes varying from cloudy swelling to complete necrosis of the epithelium of the convoluted tubes. He noted the fatty changes and described structureless masses that were always present in cases with marked necrosis. He drew attention to the hyperemia of the glomeruli, and pointed out that the capsular space occasionally contained a small quantity of exudate.

Da Rocha Lima,⁹ in describing a more or less pronounced nephrosis noted the presence of calcareous concretions in the interior of the tubules, similar to those observed in cases of mercury poisoning.

Blair, Aitken, Connal and others¹⁰ drew attention to the congestion and dilatation of all the vessels, to edema and hemorrhages between the tubules, which often contained colloid material, to fatty degeneration, swelling of the cells of the convoluted tubules, desquamation and hemorrhage in the capsular space of the glomeruli, and to changes in the convoluted tubules distant from the glomeruli.

Torres,¹¹ in a case of yellow fever, noted edema of the capsular space, swelling and desquamation of the cells of Bowman's capsule, intense fatty degeneration of the epithelial cells of the convoluted tubules and hyaline and hemorrhagic casts in the interior of the straight tubules and Henle's loops. He also pointed out that although some of these loops showed extensive necrosis and desquamation of their cells, the cells accumulated in the interior of the loops, in groups resembling endothelial leukocytes, sometimes became intensely blue when stained with hematoxylin, as if they had been saturated with calcareous salts. Referring to Hoffman's¹² observations on these casts during the Havana epidemic of 1906-1909, he emphasized the fact that in the case which he himself had seen they occupied scarcely two or three tubes in each section.

Klotz,⁵ in his reference to yellow fever in West Africa mentioned the absence of inflammation of the kidneys. He also noted the degen-

8 Elliott, C. A. Clinical Study of Yellow Fever, *Arch. Int. Med.* **25** 174, 1920.

9 da Rocha Lima, A. *Folia med.* **7** 169, 1926.

10 Blair, A., Aitken, A., Connal, and others. *Tr. Roy. Soc. Trop. Med. & Hyg.* **20** 166, 1926.

11 Torres, A. M. *Mem. do Inst. Oswaldo Cruz* **19** 13, 1926, *Sociedade de Brasileira de Biologica* **102** 414, 1929.

12 Hoffman, W. H. *Scienca med.* **6** 153, 1928.

erative changes affecting not only the convoluted tubules, but also Henle's loops and occasionally the collecting tubules, very extensive necrosis in some cases, great irregularity in the amount of fat and congestion and desquamation of the cells of Bowman's capsule. Hudson¹³ observed swelling and necrosis of the tubular epithelium, fatty degeneration, congestion of the small vessels and in particular of the glomeruli, debris, hyaline, granular and calcareous casts in the lumina of the tubules, dilatation of Bowman's capsule, with the presence in its interior of granular material, and the absence of hemorrhage and inflammation.

The changes described by Councilman⁴ forty years ago were observed in my cases. The hyaline and granular degeneration that he described as being the principal change in the cells of the convoluted tubules was found to be the dominant lesion in my cases, both because of its intensity and because of the frequency of its occurrence. My observations differed from those of Councilman, however, with respect to the presence of leukocytes, which he found and interpreted as a manifestation of an inflammatory reaction. I found no trace of leukocytes in any of my cases.

The necrosis described by Elliott,⁸ Klotz,⁵ Torres¹¹ and Hudson¹³ was found in my cases, though I did not note any predilection for the cells of the convoluted tubules. In the majority of cases, the necrosis was sparsely and irregularly distributed, involving cells of the various structures of the kidneys. The fatty degeneration noted since Councilman's day which Marchoux and Simond observed to be of varying intensity, I found, in the majority of my cases, to be very mild. Klotz⁵ emphasized the great irregularity of the amount of fat and called attention to the disproportion existing between the intensity of the degenerative processes and the amount of fat found. This disproportion, as I have already pointed out, was definite in my cases.

Councilman⁴ noted the presence of crystalline masses, at times with lines of fractures radiating from the center toward the periphery. These were evidently calcareous casts. I cannot understand why he found them yellow or greenish-yellow and resistant to the reagents used, since it is known from the work of others that they can be stained a vivid blue with hematoxylin. I saw them thus in my cases, frequently with the radiations from the center toward the periphery, to which Councilman referred. With regard to the frequency of these deposits, I found them in about 60 per cent of my cases, but in only a few tubules in each section, thus confirming Klotz'⁵ percentages.

13 Hudson, N. P. *Am J Path* 4:395, 1928.

and the small numbers noted by Torres¹¹ I found, also, that these casts showed iron in their composition

The congestion referred to by the majority of observers was present in all my cases, and it is important to note that it was always more marked in the medulla than in the cortex

I did not observe definite hemorrhages in my cases, but they were noted in the cases of Blair, Aitken, Connal and others,¹⁰ although not by Hudson¹³ In experimental yellow fever, Stokes, Bauer and Hudson¹⁴ reported finding extreme fatty degeneration of the majority of the cells of the convoluted tubules and at times also of the collecting tubules These investigators found hyaline, granular and calcareous casts, but not in all specimens They noted occasional congestion of the deposits and emphasized the absence of hemorrhage and inflammation

Hudson,¹³ comparing the lesions present in experimental cases with those found in cases in man, noted that the lesions occurred in much milder form in the infected monkeys

My observations confirm the reports of these investigators, except with regard to fatty changes, which were very moderate in the majority of my cases

The presence of acidophil masses, which I observed in the interior of the nuclei of cells in degeneration, in human as well as in experimental cases, was not mentioned by any of the previous investigators Stokes, Bauer and Hudson¹⁴ mentioned the presence of masses of acidophil granules in the interior of the nuclei of cells in degeneration in the liver in monkeys experimentally inoculated, and Torres described acidophil nuclear inclusions in the hepatic cells of thirty-one of forty-three infected *rhesus* monkeys Penna and de Figueiredo¹⁵ confirmed Torres' observations, finding the same inclusions in the cells of the liver in thirty-six *rhesus* monkeys, and Cowdry and Kitchen¹⁶ found them also in the liver, but only in cases of yellow fever in man

The acidophil structures which I noted differed from the inclusion bodies observed by Torres,¹¹ for, while the latter's always showed the granular structure described by him and by Cowdry and Kitchen,¹⁶ mine were more or less homogeneous and hyaline, and varied in form, being at times irregular in shape with smooth borders, but more commonly oval with convex borders This marked difference makes me think it possible that the masses I found were acidophil and swollen

14 Stokes, A., Bauer, J., and Hudson, N. P. *Am J Trop Med* 8 103, 1928

15 Penna, Oswaldo and de Figueiredo, B. *Folia med* 10 229, 1929

16 Cowdry, E. V., and Kitchen, S. F. *Intranuclear Inclusions in Yellow Fever*, *Sciencia* 69 252, 1929

nucleoli, although they did not in any way suggest nucleoli, either in their form or in their isolation in an empty and very clear space in the center of the nucleus. Torres¹¹ in describing the presence in some cells of the liver in yellow fever of nucleoli in degeneration which appeared to be acidophil and considerably swollen, advised in such cases staining by Goodpasture's method (aniline fuchsin, differentiation with alcohol) and with Löffler's alkaline blue. This stains the degenerating nuclei an intense red, and thus differentiates them from the true inclusions, which become violet blue. Using this method I observed that while the nucleoli appeared to be stained an intense red and the nuclear chromatin violet-blue, the masses referred to took neither of the two stains appearing only slightly darkened and resembling colloid material.

The nature of these masses and also of the inclusions described by Torres¹¹ is not easy to explain. It seems reasonable to suppose that they are nothing more than the result of nuclear degeneration, and that the chromatin, the nuclear fluid and often even the nucleolus (elements that combine in degeneration, assuming one aspect or another) contribute toward the formation of these masses. The fact that I encountered acidophil masses in the cells of the kidneys in cases other than those of yellow fever, but in which there was cellular degeneration, is significant and I believe that in cases of parenchymatous degeneration a more accurate investigation of the various structures of the organism and of different morbid conditions will reveal these nuclear pictures perhaps with a certain frequency, indicating nonspecific degeneration of nuclear material as indicated in the observations of Von Glahn and Poppenheimer.¹⁷

Proof that nuclei in their diverse degenerative phases can present the most varied forms may be found in the fact that in some of my cases they became entirely solidified into a homogeneous acidophil mass and afterward became disintegrated into minute fragments in the midst of the protoplasm in hyaline and granular degeneration.

CONCLUSIONS

From what has been reported it may be concluded that the kidneys in yellow fever are severely and characteristically injured, the lesions correspond in their nature and intensity to the gravity of the clinical disturbances.

While variations are found in the severity of the more definite lesions the kidney in yellow fever may from the standpoint of the

¹⁷ Von Glahn and Poppenheimer, A. M. Intranuclear Inclusions in Visceral Disease. *Am J Path* **1**: 445, 1925.

pathologic histology, he described as follows. The convoluted tubes are dilated and their cells are swollen and in a state of intense hyaline and granular degeneration. There is necrosis of some cells in the various structures, the glomeruli, with their tufts, are engorged, the capsular space is dilated, necrosis and desquamation of the cells of the epithelium covering the Bowman's capsule is observed, there is granular material or debris in the interior of a great number of convoluted tubes, hyaline, granular and calcareous casts occupy the lumina of some convoluted tubules, of Henle's loops or of the collecting tubules, there is congestion of the small vessels, most marked in the medullary zone. There is neither hemorrhage nor inflammation.

The following points are noteworthy: (1) fatty degeneration plays a minor role in the ensemble of degenerative changes, in the great majority of cases, (2) the calcareous casts contain iron, (3) some of the nuclei of the degenerating cells contain acidophil, homogeneous, hyaline inclusions, sharply isolated in an empty, clear space, (4) other nuclei show some form of degeneration as manifested by their solidification into acidophil, compact hyaline masses, breaking up afterward into innumerable granules which tend to lose their color and gradually to become fused with the mass of protoplasm, which in such cases is always found undergoing hyaline and granular disintegration.

SPONTANEOUS SCURVY IN MONKEYS*

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SAN FRANCISCO

Since no description of the spontaneous occurrence of scurvy in monkeys could be found, the following report is offered for those interested in the care of these animals

On Nov 7, 1929, a shipment of monkeys (lot 19) was received at the Hooper Foundation, San Francisco, from a dealer who had acquired the animals a few weeks previously from an English freighter from Calcutta, India During the forty days of the voyage, the monkeys were fed, so far as could be ascertained, largely on unhulled ("paddy") rice and dried beans without any greens This diet was continued at the dealer's warehouse, with the addition of vegetables once a week As the shipment appeared healthy, no particular attention was paid to the individual animals on arrival at the laboratory They were given the customary diet, which had recently been changed, however, owing to the prevalence of bacillary dysentery in a previous shipment The quantity of fruit and vegetables had been reduced, with a corresponding increase of dry food, sunflower seed, rice and barley Fifteen days later, on November 22, it was noticed that a small female, no 442 was lame, having great difficulty in climbing This animal was removed from the others and placed in a small cage for observation Four days later, on November 26, the eyelids appeared dark and markedly edematous, the gums were bleeding, a tooth was gone, and the right elbow joint was enlarged and painful to the touch The legs were moved with difficulty, and the animal uttered short cries when attempting to climb A tentative diagnosis of scurvy was made

ADVANCED CASES

Thirty-nine stock monkeys of lot 19 were then examined for clinical manifestations of scurvy The individual results are shown in table 1, and a general summary is included in table 2

Bleeding of the gums on pressure, with accompanying looseness of the teeth, was the principal symptom noticed in thirty-five of the

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thirty-nine monkeys (89·7 per cent) The gums of many were spongy or bluish Soft, cushion-like swellings on the head, usually over the frontal bone, were shown by 30·7 per cent, 20·5 per cent were lame,

TABLE 1—*Lesions Noticed in Thirty-Nine Monkeys Soon After Their Arrival*

Monkey	Bleeding Gums	Cushion Like Cranial Swellings	Swollen Eyelids	Lameness	Swollen Joints	Cushion Like Swellings of Ear	General Weakness	Manner of Death
Stoek 4	+	0	0	0	0	0	+	Killed
Stoek 5	+	+	+	+	+	+	+	Died
Stoek 6	+	+	0	+	+	0	+	Died
Stoek 7	+	0	+	+	+	0	+	Killed
Stoek 8	+	+	(old sear)	0	0	+	+	
399	+	0	0	0	0	0	0	
401	+	0	0	0	0	0	0	
402	+	0	0	0	0	0	0	
403	0	0	0	0	0	0	0	
412 (419)	+	0	0	0	0	+	0	
413	+	+	0	0	0	0	0	
414	+	0	0	0	0	+	0	
415	+	+	0	+	0	0	0	
417 (447)	+	+	(slight)	0	0	0	0	
418	+	0	0	0	0	0	0	
419	+	0	0	0	0	0	0	
420	+	+	0	0	0	0	0	
421	+	+	0	0	0	0	0	
422	+	0	0	0	+	+	+	
423	+	0	0	0	0	0	0	
424	+	0	0	0	0	0	0	
425	+	+	0	+	0	0	0	
426	+	+	0	+	0	0	0	
427 (448)	+	0	0	0	0	0	0	
428	+	0	0	0	0	0	0	
429	+	0	0	0	0	0	0	
430	+	0	0	0	0	0	0	
431	+	0	0	0	0	+	0	
432	+	(slight)	+	0	0	0	0	
433	+	(slight)	0	0	0	0	0	
434	0	0	0	0	0	0	0	
435	+	(slight)	0	0	0	0	0	
436	+	(slight)	0	0	0	0	0	
437	0	0	0	0	0	0	0	
438	+	0	0	0	0	0	0	
439	0	0	0	0	0	0	0	
441	+	(slight)	+	(old sear)	0	+	0	
442	+	0	+	+	+	0	+	

* + = lesion present, 0 = lesion unnoticed

TABLE 2—*Summary of Lesions in Thirty-Nine Monkeys at Time of Arrival*

Lesions	Number	Per Cent
Bleeding gums	35	89·7
Cushion like cranial swellings	12	30·7
Swollen eyelids	3	7·6
Cushion like swellings of ear	6	15·3
Lameness	8	20·5
Swollen joints	4	10·2
Deaths	3	7·6
Recoveries	36	92·3
Combination of several symptoms	19	48·7

especially in the hip joints, 10·2 per cent had greatly swollen joints, 15·3 per cent showed soft swellings on one or both outer ears, or else the tissue was shrunken or wrinkled, indicating the absorption of an old hemorrhage, three, or 7·6 per cent, died within a few days Two of the latter showed symptoms of advanced scurvy but also had a

complication of bacillary dysentery (Flexner type), while the third died of septicemia due to a large abscess on the back following a ruptured hemorrhagic area along the spine. Another animal (stock M7) was weak, thin and unable to climb, so that it was killed on Dec 3 1929.

The details of the postmortem observations in three monkeys (nos 5, 6 and 7) are given in the following paragraphs.

M Stock No 5—On Dec 1, 1929, the animal died during the night. Extensive subperiosteal hemorrhages were found around both shoulder joints. The head of the right humerus was rough and eroded. Hemorrhages were noted along the muscle sheaths of both arms down to the elbows. Extensive subperiosteal hemorrhages were present over the whole frontal bone of the skull. The eyelids were greatly swollen. The liver was pale and patchy. The spleen was spongy, soft, dark red and bulging, when cut. The pancreas was normal, the kidneys were pale, the heart was enlarged. A few petechial hemorrhages were seen on the outer wall of the colon, but no definite mucosal ulcers. The Flexner type of dysentery organism was isolated from the colon.

M Stock No 6—The animal died during the night of Dec 3, 1929. It had been thin and emaciated, unable to climb easily and lame, it showed bleeding from the gums. The liver was pale, the spleen was dark red and spongy, the kidneys were pale, the lungs were normal. The heart was large, the myocardium, soft. Small petechial hemorrhages were present on the outer wall of the colon. The Flexner type of dysentery organism was isolated from the colon. Subperiosteal hemorrhages with subsequent clotting were observed around the heads of both humeri and of both femurs. No hemorrhages into the joints were noted, but the long bones were eroded and easily broken at the upper epiphyses. An extensive subperiosteal hemorrhage covered the entire frontal bone, while a small blood clot was present above the dura. The gums were congested, and there was bleeding from the front incisors.

M Stock No 7—The monkey had been weak and emaciated, showing difficulty in climbing. It suffered from extensive bleeding from the gums. On Dec 3, 1929, it was killed with chloroform. The peritoneal cavity was dry. The spleen was small and dark, with margins slightly rounded. The liver was mottled, its lobular structure was pronounced, the blood in the portal veins was watery, some lobuli were grayish, others slightly yellowish. The lungs were normal. The myocardium was flabby. The lymph nodes showed blackish pigmentation. Intramuscular and subperiosteal hemorrhages extended along the left humerus, with marked erosion at the epiphyses and the joint surfaces. Intramuscular hemorrhages also extended along the right arm. The same hemorrhagic condition and erosion of the bone were present in both femurs. Extensive hemorrhage was present over the whole frontal bone of the skull. There was bluish discoloration of the gums. Petechial hemorrhages were seen along the outer wall of the colon, but no dysentery organism was isolated, because the cultures were overgrown by *Bacillus proteus*.

HEALING CASES

Since the clinical and postmortem observations were those of scurvy the diet of the monkeys was changed to correct the vitamin deficiency. Each animal was given one fourth of an orange every day, with raw cabbage and bananas twice a week. Carrots were included once a

week, with a daily ration of sunflower seed alternating with rice and barley. Marked improvement was soon noticed in the condition of the animals. Their appetites increased. They could run about and climb more readily. There was less bleeding from the gums, and the swelling of the eyelids and of the joints decreased.

During the next few months all of these animals were used for other experimental work, but were occasionally examined for any abatement of the symptoms of scurvy. The soft subperiosteal swellings over the cranial bones and the hemorrhagic swellings of the ears were slower to disappear than the other manifestations, but were entirely gone when most of the animals were put to death. Absorption of the hemorrhages in the ear resulted in a dried and wrinkled condition of the tissue, giving the outer ear an irregular, deformed appearance while absorption of the cranial hemorrhages occasionally left a shallow depression in the skull bone.

Two monkeys (nos 425 and 442) were studied more carefully than the others. One of these animals (no 442) presented advanced scurvy, while the other (no 425) showed only slight symptoms. Several roentgenograms were taken during life, the diagnoses being made by Dr H. E. Ruggles and Dr R. S. Stone of the University of California Hospital. The histories of these two monkeys are as follows:

MONKEY 425—The animal was a medium-sized male monkey of the species *Macacus rhesus*.

Nov 29, 1929. The monkey was lame in the left leg, showed a soft swelling of the cranium and bleeding along the upper front gums. It was given oranges and cabbage with the diet.

December 9. The animal was improved, but still slightly lame. X-ray pictures were taken; they showed a slight irregularity in the epiphyseal lines at the lower ends of both femurs and at the upper epiphyses of the right humerus.

December 26. The animal was much improved, no lameness nor bleeding of the gums was noted.

Jan 9, 1930. The animal was very active. X-ray pictures showed increased calcification about the upper end of the right humerus.

February 11. The monkey was in good condition, its fur was smooth; there were no cranial swellings, and the animal was lively. X-ray pictures showed improvement in the bone changes.

March 20. The monkey was given an intracranial injection of poliomyelitis virus.

March 30. The animal was paralyzed, and died during the night.

Postmortem Examination—The heart was enlarged, the kidneys normal, the spleen pale, the liver yellowish with rounded margins, the pancreas and intestines normal. A slightly healed subperiosteal hemorrhage was present over the right frontal bone and there were no signs of active hemorrhages in the long bones.

MONKEY 442—The animal used was a small female monkey of the species *Macacus rhesus*.

TABLE 3.—*Appearance of Monkeys at Necropsy*

Monkey	Date of Death	Time Since First Examination, Days	Lesions Noticed at Necropsy*					Cause of Death (Killed)
			Bleeding Gums	Cranial Hemorrhages	Lesions of Ear	Increased Mucoid Joint Fluid	Other Hemorrhages and Conditions Noticed	
Stock 4	11/29/29	2	+	0	0	0		Dysentery, scurvy
Stock 5	12/ 1/29	1	+	1 (fresh)	1	+	Hemorrhages around shoulders, along muscle sheaths of arms, creoson of right humerus	
Stock 6	12/ 3/29	6	+	1	0	1	Hemorrhages around heads of humeri and femurs	Dysentery, scurvy
Stock 7	12/ 3/29	6	+	1	0	0	Intramuscular and subperiosteal hemorrhages along humeri	(Killed)
Stock 8	1/2/30	37	0	1 (healed)		1 (left knee joint)	Creoson at head of right humerus	Tuberculosis
999	1/30/30	61	(congested)	0	0	0		Pohomyelitis
101	1/27/30	61	(congested)	+	0	0	Spongy, hemorrhagic condition at head of left humerus	Pohomyelitis
102	1/28/30	62	0	0	0	0		Pohomyelitis
403	1/30/30	61	0	0	0	0		
112 (149)	2/11/30	73	0	1 (healed and absorbed)	(Wrinkled)	0	Healed, absorbed hemorrhages at heads of humeri and left elbow joint	
113	2/19/30	81	0	0	0	1 (right knee joint)		Pohomyelitis, tuberculosis
114	1/14/30	48	0	1 (healed)	(Wrinkled)	0	Head bones soft and spongy	Pohomyelitis
115	1/ 2/30	36	0	+	0	+	Large callous at head of left femur, jelly like substance between muscle sheaths of right leg, and around head of left humerus	Pohomyelitis
116	1/16/30	70	0	0	0	0		Pohomyelitis
117 (147)	1/15/30	49	0	1 (healed)	0	1 (right elbow joint, right shoulder joint)	Healed hemorrhagic area along right humerus	Pohomyelitis
118	2/14/30	79	0	0	0	0	Continuous subcutaneous exudate along right arm, head of right humerus enlarged and calcified	Pohomyelitis, tuberculosis
119	3/16/30	139	0	0	0	0		Pohomyelitis

420	1/29/30	152	0	0	0	0	0	0	Polomyelitis, tuberculosis
421	2/12/30	77	0	+	0	0	0	0	Polomyelitis
422	2/1/30	68	0	+	0	0	+	0	Polomyelitis
423	5/28/30	182	0	0	0	0	0	0	Polomyelitis
424	1/1/30	125	0	0	0	0	0	0	Polomyelitis
425	3/30/30	120	0	1	0	0	0	0	Polomyelitis
426	2/1/30	78	0	0	0	0	0	0	Tetane spasmus
427 (18)	2/11/30	76	0	0	0	0	0	0	Polomyelitis
428	3/5/30	128	0	0	0	0	0	0	Polomyelitis
429	1/10/30	44	(congested)	0	0	0	0	0	Flexner dysentery
430	4/25/30	149	0	0	0	0	0	0	Tuberculosis
431	2/26/30	91	0	+	0	0	0	0	Tuberculosis
432	3/4/30	127	0	+	0	0	+	0	Tuberculosis
433	3/18/30	111	0	0	0	0	0	0	Tuberculosis
434	2/1/30	69	0	1	0	0	0	0	Dysentery, tuberculosis
435	2/1/30	78	0	0	0	0	0	0	Experimental polomyelitis
436	1/21/30	65	0	(bone porous)	0	0	+	0	Polomyelitis
437	12/17/30	20	0	0	0	0	0	0	Pneumonia
438	2/19/30	84	0	0	0	0	0	0	Polomyelitis
439	1/29/30	63	0	0	0	0	0	0	Polomyelitis
441	12/9/30	12	0	0	0	0	0	0	Abscess of back
442	4/30/30	151	0	+	0	0	+	0	Polomyelitis
				(almost no trace)			(slight, in shoulder joints)		

* + = lesion present, 0 = no lesion noticed

Nov 22, 1929 The monkey was lame in both legs, showing great difficulty in climbing

November 26 The gums were bleeding, one tooth was gone, the eyelids were extremely swollen, and the right elbow joint was enlarged and painful. The animal was fed the juice of one orange

November 27 The eyelids were much improved, swelling was reduced, although evidences of subcutaneous hemorrhages were still noticed. Much difficulty was experienced in climbing because of the swollen right elbow and knee joint. The diet was changed to correct the vitamin deficiency

December 9 The animal was much improved, climbing more easily. X-ray pictures showed subperiosteal hemorrhages about the shafts of both humeri and of



X-ray pictures of monkey 442. *A*, x-ray picture taken on Dec 9, 1929, note the subperiosteal hemorrhages around the upper ends of both humeri. *B*, x-ray picture taken on Jan 9, 1930, showing marked calcification around the heads of both humeri. *C*, x-ray picture taken on April 29, 1930, showing increased calcification around the heads and along the shafts of both humeri.

both femurs, with irregularity at the upper epiphysis and of the shafts of both humeri and of the lower end of the left radius (fig *A*)

December 26 The monkey was greatly improved climbing around easily although there was bleeding of the gums above the upper incisors

Jan 9, 1930 There were no swollen joints, and much improvement was noted. X-ray pictures showed a large amount of calcification in the subperiosteal hemorrhages of both humeri (fig *B*)

January 10 The animal had no bleeding of the gums, but had lost the lower right canine and premolar teeth. It could climb easily

February 11 The animal was in good condition ate well, showed smooth fur and climbed easily

April 29 X-ray pictures showed a large amount of calcification at the upper ends of both humeri (fig C)

April 30 The animal was bled to death from the heart after it had convalesced from an attack of experimental poliomyelitis

Postmortem Examination—The animal was in very good condition There was no bleeding from the gums There were signs of healed and absorbed subperitoneal hemorrhage over the entire frontal bone, and enlargements of the bone at the head of both humeri, with a slight amount of mucoid synovial fluid within both shoulder joints There were no signs of hemorrhages around the long bones The lungs, heart and kidneys were normal The liver, spleen and pancreas were pale, owing to the bleeding from the heart The intestinal wall was normal and free from ulcers or hemorrhages

COMMENT

All of the monkeys in lot 19 either died or were killed at various times during the six months from the early part of December, 1929, to the end of May, 1930 Table 3 shows the date of death, the length of time since the first examination and an outline of the postmortem observations in respect to scurvy The latter may be compared with the results as given in table 1 for the first physical examinations

With the exception of those animals that died during the first few days (nos 4, 5, 6 and 7), none of the monkeys showed active bleeding from the gums at autopsy, or any active hemorrhages in the long bones Evidence of healed and absorbed subperiosteal hemorrhages were noticed in eleven monkeys, six of which had not previously shown any signs of the cushion-like cranial swellings (monkeys 401, 412, 414, 417, 434 and 442) These swellings had been noticed in the other five animals, but they were absorbed and in the process of healing five weeks later, at the least Similarly in monkeys 412 and 414, the tissue of the outer ear had become wrinkled and shrunken, while in monkeys 422 and 432 the ear swellings had entirely disappeared within from two to four months, respectively Seven of the group showed a slightly increased mucoid synovial fluid within some of the joints after from one to four months, indicating that the subperiosteal hemorrhages of the long bones were still being absorbed

Exclusive of monkeys 5, 6 and 7, none of the animals was lame at the time of death Twelve of thirty-six showed evidence of healed and absorbed hemorrhages either in the subperiosteum or between the muscle sheaths around the ends of the long bones The epiphyses were often fragile, fracturing easily Monkey 421 showed an enlarged callus at the head of the humerus (seventy-seven days after the first examination), while the same appearance was seen around the head of the left femur of monkey 415 (thirty-six days) and at the proximal ends of both humeri of monkey 442 (forty-three days) There was

an extensive gelatinous subcutaneous exudate along the right arm of monkey 418, suggestive of a former widespread hemorrhagic condition which was slowly being absorbed (seventy-nine days after the first examination). It was interesting to observe that after dietary treatment excessive calcification developed subsequent to absorption of the hemorrhages around the long bones. This is well illustrated by the x-ray pictures of monkey 442. During the acute hemorrhagic stage (shown in *A*), the bone structure of both humeri appeared normal in size, surrounded by a soft layer of blood. In the later pictures (*B* and *C*), an increasing amount of calcification was clearly demonstrated until the bone shaft was completely distorted.

The character and extent of the lesions in this group of monkeys both during life and at postmortem examination, with the evidences of marked improvement on dietary treatment alone, fully confirmed the original diagnosis of scurvy. The prompt response to orange juice and cabbage, both rich in vitamin C, was most encouraging, as well as confirmatory.

After each autopsy, the animal's head was removed and given to Dr. Hermann Becks for a detailed examination of the dental condition, while the long bones of several monkeys were given to Dr. Moritz Weber for a microscopic examination of the bone structure. Separate reports of their observations will be given later.

Harden and Zilva¹ found that scurvy could be produced in monkeys in about two months, and that protection from the disease resulted on feeding from 2 to 5 cc of orange juice per day. This period of development corresponds with that presumably occurring in the case of the monkeys of lot 19, forty days being allowed for the voyage and the three or four weeks' interval before the diagnosis was made. In 1924, Howe² also produced scurvy in monkeys, but was mainly interested in the dental aspects of the disease.

The most extensive and detailed description of experimental scurvy in monkeys is that of Hart,³ who in 1912 induced the disease by feeding condensed milk. His description of the clinical manifestations corresponds closely to the observations recorded for lot 19. He stated that the animals gradually lost their liveliness and showed a loss of appetite, while their movements became slow and cautious. The limbs were painful to the touch, as was manifested by their short cries and jerky motions. Bleeding gums appeared early, although in no case was there an ulcerative stomatitis. The gums finally showed diffuse bluish-

1 Harden and Zilva. *Biochem J* **14** 131, 1920.

2 Howe. *J Am Dent A* **11** 1161, 1924.

3 Hart. *Arch f Kinderh* **76** 507, 1912.

red swelling. Cushion-like swellings were observed on the skull, as well as intense, but quickly retrogressing, exophthalmia with hemorrhage of the upper eyelids. Swellings of the epiphyseal ends of the long bones and fractures, especially in the lower part of the femur and the upper part of the humerus, were frequently observed. Hemorrhages between and into the muscle bundles were often present, and extravasated blood could be found in the meninges, lungs, kidneys, and intestinal mucosa. Occasionally there was blood in the proximity of the epiphyseal endings of the long bones, while a complete casing of blood was often seen around the femur and the humerus, extending from the proximal to the distal articulations. Severe changes were noticed in the jaw bones, with a bloody suffusion of the gums. He also noticed occasional subperiosteal hemorrhages of the orbital roof, of the ribs and of the bones of the skull, and bleeding around the optic nerve. The bones, especially those of the jaw and skull, were often severely eroded and very friable.

Similarity between the clinical pictures of the experimental and the spontaneous development of scurvy in monkeys is thus readily observed.

SUMMARY

A report is given of the spontaneous development of scurvy in a group of thirty-nine monkeys (*Macacus rhesus*) received from India. The diagnosis was made from the clinical symptoms, the x-ray pictures and the postmortem observations, all of which corresponded closely to the description given by Hart of experimental scurvy in monkeys. A change of diet to one rich in vitamin C produced marked improvement within a few weeks, with subsequent complete recovery, in all of the group, except those presenting advanced scurvy which were put to death or which died during the first few days.

THE SIMILARITY OF PSEUDOTUBERCULOSIS AND TULAREMIA ¹

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In 1916, Roman ¹ working in Prague, published the complete report of a case that he classified as one of an unusual form of infectious granuloma. Clinically, little was known of the case, but at autopsy the condition appeared at first to be tuberculosis. Because of the atypical histologic observations and the isolation of a nonacid-fast bacterium from the lesions, the condition was classified as "pseudotuberculosis."

Pseudotuberculosis is a term first used by Eberth in 1885 in describing a rare tuberculosis-like disease in guinea-pigs ² and rabbits ³. Eberth's descriptions of the pathologic changes in the liver and spleen are almost identical with those of Roman, and the changes appear to have been caused by an organism similar in many respects. The isolation and description of *Bacillus pseudotuberculosis* was first accomplished by Pfeiffer in 1889 ⁴. Since then numerous cases of pseudotuberculosis have been reported, chiefly from European sources. From many of the older case reports, however, it is difficult to arrive at definite conclusions in regard to etiology on account of the inadequate descriptions or antiquated methods employed for bacteriologic identification.

CLINICAL AND PATHOLOGIC OBSERVATIONS, AS RECORDED

BY ROMAN

Roman's patient was a railroad employee, aged 46. He was admitted to the hospital in a moribund condition and died the next day. From his wife it was learned that ten days previously he first noticed fever, which gradually increased. There was severe pain in the region of the liver, radiating to the chest. Anorexia and moderate constipation were noted. The day before admission, the patient became delirious. No jaundice was noted.

* Submitted for publication, Sept 23, 1930.

¹ From the University of Minnesota Medical School, Minneapolis and the Buffalo General Hospital and School of Medicine, University of Buffalo.

1 Roman, B. Virchows Arch f path Anat **222** 53, 1916.

2 Eberth, C J. Virchows Arch f path Anat **100** 15, 1885.

3 Eberth, C J. Virchows Arch f path Anat **103** 488, 1886.

4 Pfeiffer, A. Ueber die Bazillare Pseudotuberkulose bei Nagetieren, Leipzig, 1889, cited by Roman.

Physical examination revealed a well developed, well nourished man. The abdomen was tense and very tender. The margin of the liver was a hand's breadth below the costal margin and was very tender on palpation. Its surface appeared to be smooth. The spleen was not palpable, but was slightly enlarged to percussion. The pulse rate was 132. The temperature varied from 37.8 to 40.2 C (100 to 104.4 F). The blood count showed leukocytes, 6,800, neutrophils, 60 per cent, transitional forms and large mononuclears, 20 per cent, lymphocytes, 17 per cent, and eosinophils, 3 per cent.

The important pathologic features described by Roman are as follows:

The liver measured 32 by 28 cm, and weighed 3,400 Gm. The surface was uniformly studded with many nodules, from hempseed size to bean size. They were mostly pea-sized, and were gray and moderately firm. Many appeared to be umbilicated. The cut surface showed similar nodules, which were sharply circumscribed and grayish white or yellow. Many seemed to be softened in the center and collapsed. The liver tissue between the nodules was grayish brown and firm. The spleen weighed 600 Gm and measured 20 by 12 by 8 cm. It was soft, and the capsule was slightly thickened. The cut surface was dark red, and the markings were indistinct. The lymph nodes near the lesser curvature of the stomach were walnut-sized. Similar nodes were also found in the mediastinum and around the abdominal aorta. The duodenal lymph follicles were prominent. Several plaques and solitary follicles were found in the ileum. The margins were swollen in some and in others appeared to be somewhat sunken and grayish white.

Histologically, the liver showed generalized cirrhotic changes with extensive alteration and regeneration. There was a large amount of iron-containing pigment in large and small clumps in the parenchymal cells and in the connective tissue. The nodules appeared as sharply demarcated, round, darkly staining areas, which at first glance might be taken for tubercles or gummas. They consisted of granulation tissue in various degrees of necrosis. Polymorphonuclear leukocytes were rarely seen. Karyorrhexis was commonly found. In the center of the nodules, cell clumps, chromatin debris and pigment were recognizable. Giant cells of the Langhans type were not encountered. Foci that resembled giant cells were occasionally found. These areas stained dirty blue with hematoxylin, on closer examination with a higher power they proved to be clumps of bacteria. Such areas were found especially near the periphery of the nodules. Bacteria were never seen outside of the nodules. A smear made from the liver showed many gram-negative bacilli of varying length and breadth, but mostly short plump rods.

Histologically, the intestines showed general atrophy of the wall involving all layers. In many sections, the mucous membrane was entirely absent. The lymphoid tissue had for the most part disappeared. In sections from the plaques, no gland tissue could be seen.

BACTERIOLOGIC AND EXPERIMENTAL STUDIES

Roman then cultivated portions of the spleen and liver on Drigalski plates, and after twenty-four hours obtained a rich growth of small, round, blue colonies composed of gram-negative, nonmotile, short bacilli. A guinea-pig inoculated subcutaneously with the culture died fifteen days later. Autopsy showed generalized necrosis of the abdominal wall at the site of injection. The liver was riddled with submiliary to pin-

head-sized, grayish-white nodules. There were similar but fewer nodules in the spleen, one in the right suprarenal gland and several in both lungs. Histologically, the nodules were identical with those described in a preceding paragraph. The bacilli were recovered in pure culture from the heart blood.

The bacilli were gram-negative and aerobic and did not form capsules or spores. They were mostly short rods, some appearing to be almost coccidial. There was considerable variation in size. Bipolar staining was occasionally seen in older cultures. They grew well on agar, reaching the maximum colony size in forty-eight hours at 37 C. The colonies were grayish, moist and glistening. Growth occurred after twenty-four hours in gelatin stab cultures. Agar was not liquefied. Bouillon was slightly clouded after twenty-four hours and showed a floccular precipitate. Peptone water was quickly clouded and a heavy sediment formed. Indol was not formed. Growth also occurred in milk, on potato, in Loeffler's coagulated serum and on human blood agar (without hemolysis). No gas was formed in mediums containing 1 per cent grape sugar.

EXPERIMENTS ON ANIMALS

The bacteria were pathogenic for guinea-pigs, rabbits and white mice and occasionally for pigeons when injected subcutaneously. Rats and chickens were not susceptible. All feeding experiments gave negative results. Pathologic changes like those described in foregoing paragraphs were encountered in most animals succumbing to the infection. The typical histologic changes were in the form of granulomas but these differed from tuberculosis. The process of destruction did not resemble the cheesy necrosis of tuberculosis or the marked karyorrhexis noted in glanders. Like most of the other observers Roman failed to find giant cells in the nodules.

Roman cited the case reports of ten other observers. The cases of Lorey⁵ and Saisawa⁶ seem to be the most typical. Lorey's case was diagnosed clinically as possibly a case of typhoid fever. The patient died after eleven days, and necropsy revealed a large liver studded with typical nodules. Lorey cultivated a bacillus from the patient's blood during life and again at autopsy, which was identified with Pfeiffer's *B. pseudotuberculosis*. Experiments in animals gave the usual picture of the formation of typical nodules in the liver and spleen.

The case of Saisawa was that of a young soldier in Japan. (It is of interest to note that tularemia has recently been identified with

5 Lorey, A. Ztschr f Hyg 68 49, 1911

6 Saisawa, K. Ztschr f Hyg 73 353, 1913

Ohara's disease occurring in Japan⁷ Saisawa's patient also died after eleven days, and autopsy revealed nodules in the liver, but attention was chiefly drawn to the intestine. Peyer's patches were hypertrophied and ulcerated as in typhoid fever, and the regional lymph nodes were swollen. A bacillus corresponding to *B. pseudotuberculosis* was cultivated from the blood and pericardial fluid. The results of the experimental studies were similar to those described by Roman and Loiey.

The origin of infection in both of the aforementioned cases was obscure. In only one report found in the literature does the author suggest the possibility of infection from a cat. Contact with rabbits or other rodents is not mentioned, nor are cases of laboratory infections mentioned.

Epizootics of pseudotuberculosis among guinea-pigs have been recorded. Tahssin-Bey⁸ described an epizootic caused by a gram-negative bacillus classified as *B. pseudotuberculosis rodentium*. Autopsy showed chiefly an involvement of the lymph nodes. The lymph nodes, spleen and liver contained nodules from which the bacillus could be recovered in pure culture. The disease could be transmitted to other guinea-pigs by inoculation or by rubbing infected material on the mucous membranes. Rabbits were apparently not as susceptible to infection as guinea-pigs.

A similar epizootic was described by Gaté and Billa.⁹ Guinea-pigs died six or eight days after infection. The liver and spleen were usually enlarged and studded with tubercles. Tubercles were also encountered in the lungs, but no acid-fast bacilli were found. In these animals there were multiple mesenteric abscesses. The intestinal mucous membrane was congested, and Peyer's patches were hypertrophic. They also demonstrated a gram-negative bacillus in the lesions, and obtained it in pure culture. There was some difficulty in cultivating the organism satisfactorily. Its morphology varied according to the medium on which it grew. They classified it with Pfeiffer's *B. pseudotuberculosis*.

Other European investigators have studied the relationship between *B. pseudotuberculosis* and *B. pestis*¹⁰ and other bacilli.¹¹ There are apparently some points of resemblance in fermentation and cross-immunity reactions, but the marked differences in pathogenic behavior should not lead to confusion. The similarity between *B. tularensis* and *B. pestis* has also been noted.

7 Francis, E., and Moore, D. Identity of Ohara's Disease and Tularemia, J. A. M. A. **86** 1329, 1926.

8 Tahssin-Bey, S. Centralbl. f. Bakteriologie (Abt. 1, O.) **102** 374, 1927.

9 Gate, J., and Billa, M. Compt. rend. Soc. de biol. **99** 812, 1928.

10 Zlatogoroff, S. J. Centralbl. f. Bakteriologie (Abt. 1, O.) **37** 513, 1904.
MacConkey, A. J. Hyg. **8** 335, 1908. Arkwright, J. A. Lancet **1** 13, 1927.

11 Haupt, H. Centralbl. f. Bakteriologie (Abt. 1, O.) **109** 1, 1928.

COMMENT

The striking similarity of the clinical histories and pathologic reports of cases of pseudotuberculosis described by Lorey, Saisawa and Roman to the descriptions of tularemia, particularly that of the "typhoidal" type, suggests the possibility of a relationship between the two diseases. Poppe¹² suggested that tularemia may be a form of human pseudotuberculosis. Tularemia has been recognized in Russia and in Scandinavia, and there seems to be no reason for its nonexistence in central Europe, from which no cases have been reported. Francis,¹³ however, holds that tularemia and pseudotuberculosis are different diseases and have not been mistaken for one another in Europe.

Experiments on animals with *B. pseudotuberculosis* for the most part closely parallel similar experiments with *B. tularensis*. The same animals are susceptible, and similar lesions are found grossly and histologically. Of particular interest is the absence of typical giant cells in the nodules in both diseases.

The descriptions of the morphologic and cultural characteristics of *B. pseudotuberculosis* and *B. tularensis* show a close resemblance. The chief points of difference lie in the failure to cultivate *B. tularensis* on ordinary mediums or to demonstrate the organisms in sections or smears from human tissue.¹³ However, since the beginning of 1928 only five records of postmortem examination in fatal cases of tularemia in man have appeared. It is possible that further examination in other cases may still reveal the presence of bacilli in human lesions.

Final proof of the relationship or nonrelationship between the two diseases can only be obtained by bacteriologic and serologic studies. We have attempted to obtain the organism isolated by Roman, which was sent to a culture collection for preservation. Unfortunately, the strain was lost in 1917. However, the strain of *B. pseudotuberculosis* isolated by Pfeiffer, with which Roman's strain appeared to be identical, was obtained, and experimental studies are now in progress.

CONCLUSION

Attention is drawn to the similarity between the granulomatous infection classed as pseudotuberculosis in Europe and tularemia.

12 Poppe, K. Pseudotuberkulose, in Kolle, Kraus and Uhlenhuth. Handbuch der pathogenen Mikroorganismen, Jena, G. Fischer 1927 vol 4, p 413.

13 Francis, E. Personal communication to the author.

PRIMARY TUMORS OF THE TRACHEA

REPORT OF A CASE AND REVIEW OF THE LITERATURE^{*}

RIGNEY D'AUNOY, M D
AND
ADELAIDE ZOELLER, M D
NEW ORLEANS

The first recorded observation of a tracheal tumor was that of Lieutaud in 1767. In 1861, Tuerck first observed such a new growth by means of a laryngeal mirror. From that time, with the introduction and general use of the laryngoscope, reports of tracheal new growths became relatively more frequent. Still, at this date, even with the use of improved mechanical means for direct observation of various parts of the respiratory tract, primary tracheal tumors are infrequent enough to warrant reporting any observation thereof. It is this fact that prompts the present report and survey of the literature.

REPORT OF CASE

J S, a laborer, 23 years of age, complained of difficulty in breathing that had endured for six months. Examination revealed a tracheal growth. Open operation under infiltration by procaine hydrochloride by Drs Dupuy, McNair and Fernandez showed the growth attached to the anterior tracheal wall at the fourth and fifth rings. The tumor was removed, and the patient made an uneventful recovery. Twenty months after operation, he was in good health with no evidence of recurrence.

The specimen consisted of an irregular mass of tissue about the size of a cherry. Externally it was grayish pink, and in consistency rather soft. One surface, evidently that of attachment, showed a few small pieces of cartilage embedded in the mass. Surfaces revealed by sectioning showed a homogeneous pinkish-gray color, with no special features.

Microscopic observation of sections stained with hematoxylin-eosin and by Mallory's connective tissue method proved the tumor to be an adenocarcinoma, most probably having its origin in a mucous gland.

FREQUENCY OF TUMORS OF THE TRACHEA

Semon stated the frequency relation of laryngeal to tracheal tumors as 100:1. Von Bruns reported observation of 300 laryngeal and 7 tracheal growths. Moritz Schmidt studied 2,088 new growths of the upper air passages, 748 of which were laryngeal and 3 tracheal. Mackenzie is mentioned as having seen 4 cases of tracheal tumors and 800 laryngeal new growths over a period of sixteen years. Statistics of the pathological Institute of Basle over a period of thirty-five years

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^{*} From the Department of Pathology of the Charity Hospital.

showed, out of a total of 1 078 malignant growths, 1 tracheal and 9 laryngeal involvements. At the Charity Hospital of New Orleans, over a period of twenty-three years (1906-1929), 68 laryngeal new growths and 1 tracheal tumor were observed.

Even the total number of primary tracheal growths recorded is relatively small. Thus, in 1898, von Bruns was able to collect only 147 cases from the literature, Krieg, in 1908, 201 cases, Lombard and Baldenweck, in 1914, 252 cases. Our search of the literature through 1929 allows us to add 99 cases, including the case herein reported, as well as some omitted by previous reviewers, making a total of all types of primary tracheal new growths on record of 351.

TABLE 1—*Number of Tumors of the Trachea Found Recorded by the Different Reviewers*

	von Bruns 1898	Krieg 1908	Lombard and Baldenweck 1914	D'Aunoy and Zoeller 1929
Nonmalignant				
Fibroma	23	25	29	33
Papilloma	34	41	51	59
Lipoma	3	4	5	5
Chondroma, osteoma, tracheo- pathia osteoplastica	29	42	47	65
Adenoma	5	6	6	8
Lymphoma	2	2	2	3
Intratracheal goiter	7	14	19	25
Amyloid tumor			1	2
Mixed tumors				2
Angioma			1	2
Cylindroma				1
Malignant				
Sarcoma	14	21	23	26
Carcinoma	31	40	54	91
Carcinosarcoma				1
Endothelioma				1
Histology undetermined or doubtful		6	14	27
Total	147	201	252	351

We recapitulate these cases, as well as those previously collected, in table 1, for the sake of uniformity following the presentation adopted by von Bruns and followed by Krieg and Lombard and Baldenweck, even though, as will be noted later, we do not subscribe to the inclusion of certain types of tracheal involvement in a compilation of primary tumors of the organ. With the exclusion of such cases, the number of primary tumors of the trachea recorded through 1929 is only 261.

GENERAL ETIOLOGIC CONSIDERATIONS

Naturally, no etiology can be ascribed for new growths of the trachea, although, as will be noted in the comment on some of the specific types of tumors, various theories accounting for their genesis have been advanced. Suffice it to state at this time that the infrequency of tracheal tumors is usually ascribed to the fact that the trachea is rather simple in structure and rigid, and has practically only the passive function of

acting as a passage for air. Especially, it may be pointed out, is the middle portion of the organ immovable and protected from irritating objects of all kinds, thus accounting for the greatest infrequency of the mediastinal segment as a tumor site. It appears as though the posterior tracheal wall is most frequently the point of election for tumors of all types occurring in this organ. This can probably be explained by the fact that the posterior wall is far richer in glandular structures than the anterior and lateral walls. Another possible explanation for the invasion of the posterior wall, as well as for the preference for the extremities of the organ as tumor sites, may be found in considering the distribution of the lymphatic vessels in, and their drainage of, the trachea.

BENIGN TUMORS

Fibromas—Thirty-three fibromas of the trachea have been reported. Our search revealed four cases, none of which presented unusual or interesting clinical or histologic features.

The histologic changes present in the reviewed cases varied from nodular growths to polypoid tumors, pedunculated or broad-based, and soft or firm. Small cell infiltration varied considerably, as did vascularity. Usually, the tumors were covered with epithelium, varying in thickness in different areas and at times showing cornification. Hyaline degeneration was variable in amount, although generally present. In our collected reports of cases of fibroma, we found no mention of amyloid changes or of so-called malignant metamorphosis, as noted sometimes in this type of tumor by previous reviewers.

From analysis of our statistics, as well as those collected by previous reviewers, it is evident that fibromas of the trachea occur at all ages, although they appear predominant in middle life, only three cases having been observed between the fifth and the fourteenth years. Sex incidence of tracheal fibromas is about equally divided. They have occurred in almost equal numbers in the upper and lower parts of the trachea. They have been found attached to the anterior and posterior walls about the same number of times.

Papillomas—Papillomas are the most frequently encountered of benign new growths of the trachea. We have collected eight cases, making a total of fifty-nine thus far recorded. We naturally excluded cases in which generalized papillomatosis of the larynx, as well as of the trachea, was present. The majority of the cases previously reported occurred in children, and some few were probably congenital. In our collected cases, the patients ranged in age from 7 to 63 years, with the distribution according to sex equally divided. The anterior tracheal wall presented the point of election for most of the tumors, but some occurred on the posterior and some on the lateral walls. A number of the cases presented multiple growths.

No special etiology can be ascribed for these growths, although some originated in patients who had previously worn tracheotomy tubes. Here, no doubt, trauma can be considered as a possible predisposing etiologic factor, if not a direct cause of the new growth. Tilley believed that previous gassing was etiologically important in his case.

Histologically, the tumors differed in no respect from so-called benign papillomas encountered in other areas. Essentially, they consisted of branching, poorly cellular, vascular connective tissue cores or stalks, surmounted by multiple layers of well differentiated epithelial cells, occurring in a variable number of layers, the whole giving rise to a villous or papilla-like arrangement, which, whether broad-based or pedunculated, showed no tendency to infiltration or invasion at their points of attachment.

In considering the possible malignancy of this type of tumor, we believe that the general histologic picture is relatively unimportant, and that most careful search should be made for atypical cells, atypical cell arrangement and cell invasion, with proper evaluation of such observations. That the so-called simple papillomas may evolve into tumors of entirely different character is certainly suggested by clinical data and by such experimental evidence as that adduced by Leone.

Chondromas, Osteomas, Tracheopathia Osteoplastica—We have collected one case of osteoma, one of chondroma and sixteen presenting the pathologic picture so frequently spoken of as "tracheopathia osteoplastica." In a majority of the cases, the lesions were discovered at autopsy, none apparently causing marked clinical symptoms. In six, according to the reports, tuberculosis was a coincident lesion. Nine of our collected cases occurred in men. The age of incidence was from 30 to 80 years.

We do not subscribe to the inclusion of the possible entity now so generally designated as "tracheopathia osteoplastica" in a review of primary tracheal tumors, and do so only in deference to precedent, and in order that the statistics may be comparable. For this reason, our discussion of the interesting etiologic and histologic features of this condition must necessarily be brief.

Bruckmann and others are of the opinion that not in all of these cases is the pathologic anatomy primarily associated with the tracheal cartilage, but is to be looked on as the result of developmental disturbances or anomalies in the anlage of the elastic fibers. At this time, we do not subscribe exclusively to these views, believing that the opinions expressed by Peters and others must be given consideration.

Histologically the tumors consist mostly of bone and partly of cartilaginous tissue. The latter may form projecting processes from the perichondrium or exist as narrow margins around the bony plate.

Frequently, connection between the intratracheal tumor and the cartilaginous rings cannot be demonstrated. The largest portion of bony tissue is generally attached to cartilaginous proliferations. The basic substance usually contains numerous elastic elements.

None of the tumors that we encountered under this classification showed features of special interest, histologically or otherwise.

Adenomas—We have collected two cases of adenoma which, added to the six previously recorded, make the total number of the tracheal tumors on record eight. Both cases occurred in females, one arising from the posterior wall and the other from the anterior wall.



Adenocarcinoma of the trachea

The largest number of tracheal adenomas have occurred in connection with the posterior tracheal wall. This, the anatomy of the organ being considered, could be expected. Theisen said that they originate as "hypertrophies of the mucous glands." Undoubtedly, their etiology is unknown, and their histologic features are not different from those encountered in this type of tumor when occurring in other localities. Here again careful histologic study is necessary in order definitely to rule out malignancy.

Lymphomas—Three cases are on record, our review adding one occurring in a woman 54 years of age reported by Geschelin. We take it to belong to the class of so-called simple local or regional lymphomas or lymphadenomas in which infectious processes are sus-

pected as etiologically significant. Microscopically, the growth consisted of proliferation of lymphoid tissue, with follicles, some showing multiple foci in the center, with some karyokinesis of the lymphocytes.

Intratracheal Goiters—We have collected six cases of intratracheal struma, making a total of twenty-five on record. All of the cases that we collected occurred in women from 18 to 39 years old. The posterior and lateral walls were most frequently affected.

Two theories accounting for the occurrence of this class of intratracheal growths have been advanced. Von Bruns held that in intra-uterine life aberrant embryonic rudiments of thyroid tissue become encapsulated in the tracheal and laryngeal tissues and later develop into the so-called intratracheal (or intralaryngeal) accessory thyroid glands.

Paultauf, on the contrary, asserted that these tumors originate in extra-uterine life by penetration of glandular tissue between the cricoid and thyroid cartilages, between the first tracheal ring and the cricoid cartilage, between the upper tracheal rings or even through the tracheal mucosa itself. Critical survey of the recorded material leads us to believe that both theories are correct in accounting for the genesis of this type of growth. The histology of the tumors is usually that of colloid goiter.

We do not believe, however, that cases of intratracheal struma properly belong in a collection of primary tracheal tumors and, again, only include them in deference to precedent.

Mixed Tumors—We tabulate two authentic mixed tumors, both occurring in males and the first to appear in the casuistics of tracheal tumors. One occurred in connection with the anterior tracheal wall, the other was principally attached to the posterior wall. Lynch's tumor recurred many times after removal, with later invasion of the edges of the operative wound, suggesting possible inoculation by instrumentation. Embryonal enclavements undoubtedly account for the occurrence of all tumors of this type.

Histologically, the tumors consisted of basic matrices of myxomatous material or cartilage with epithelial cell inclusions. We classify them as benign, believing that, although complex in character, no tumor of this type presents the stigmas necessary for classification as a malignant growth.

Lipomas, Amyloid Tumors, Angiomas, Cylindromas—We encountered no lipomas or amyloid tumors in our search.

Two amyloid tumors of the trachea are on record, one reported by Krause, the other by Reich. Krieg in his compilation did not mention this tumor. Lombard and Baldenweck tabulated Reich's case, but mentioned no other. Theisen in his article on tracheal tumors, mentioned

one amyloid tumor, evidently Krause's. Since both have been previously mentioned by reviewers, we tabulate neither, but present the proper number on record in our recapitulation of total cases (table 1).

One intratracheal cavernous angioma, the second recorded, was reported by Petten and Sjoval. It occurred in a woman 35 years of age, invading the trachea at its bifurcation.

A cylindroma, said by the author, Segura, to be a benign tumor developing near salivary glands and often recurring after removal, is recorded as occurring in a woman 42 years of age. It was attached to the posterior tracheal wall. Neither of these tumors presented features of particular interest.

MALIGNANT TUMORS

Sarcomas—Our search revealed three sarcomas, one spindle cell, one round cell and a fibrosarcoma, making a total of twenty-six tracheal sarcomas on record. The three tumors occurred in men from 20 to 53 years old. From the statistics it appears that sarcoma of the trachea occurs with about equal frequency in both sexes, young people being rather more frequently afflicted than persons advanced in years.

No etiology is ascribable for this type of tumor, although some authors mention malignant changes occurring in benign mesodermal growths. Kahler spoke of the possibility of a myxosarcoma originating from "displaced muscular bands" from the posterior tracheal wall.

None of the growths we reviewed presented other than the typical histology of this type of tumor.

Carcinosarcomas—Geschelin reported the occurrence of a carcinosarcoma in a man 68 years of age. It is the only tracheal carcinosarcoma on record.

The tumor consisted of epithelial elements and connective tissue, the former definitely separated from the latter and grouped in the form of massive collections of cells or simulating tubular or glandular structures. Here and there attempts at epithelial "pearl formation" could be noted. Much karyokinesis of epithelial elements occurred, especially in the cells lining the rudimentary tubular or glandular structures. The connective tissue part of the tumor consisted of little fibrillar material with many cells of various forms—round, spindle-shaped, giant. Some of the giant cells were as large as 60 microns in diameter and contained a remarkably large number of nuclei.

The interesting feature of this type of tumor of combined tissue elements is undoubtedly its histogenesis, but whether the epithelial elements develop first, and from the stroma as a result of mechanical pressure or other biochemical factors the atypical mesodermal cells develop, or whether the connective tissue element preexists with a tendency for

atypical growth of adjacent and invaded epithelial elements cannot be stated, in view of our present imperfect basic knowledge of the causation and formation of tumors. Possibly, Simmonds' theory of simultaneous growth of both elements due to the same ill-understood biochemical or other etiologic factors is the most satisfying.

Endotheliomas—Adam recorded one case of endothelioma occurring in a woman 37 years old, which originated in the anterior tracheal wall. It is the only tracheal tumor of its type on record. The specimen was given to him by a pathologist, with a diagnosis of endothelioma. Its histology is not described, and we naturally accept it as such.

Carcinomas—We are able to tabulate thirty-seven cases of carcinoma recorded since the last review, making a total of ninety-one cases on record. Of the cases we encountered, eight were squamous cell carcinomas and six adenocarcinomas, these two types constituting the largest number reported. Nine of the tumors occurred in females, twenty-one in males, in seven reports sex was not mentioned. The age distribution was from 26 to 82 years, with a preponderance (eleven cases) in the sixth decade, but with many cases (six) occurring in the fourth decade. The anterior and posterior walls were about equally invaded, with one case reported as "almost encircling" the organ. The lateral walls were invaded in numerous cases. The lower part of the organ, especially at or near the bifurcation, was invaded nineteen times. The midportion was mentioned as invaded only six times.

According to Simmel, the region of the bifurcation of the trachea is the most frequent site of carcinoma, he assumed as an etiologic consideration that at this point the mucosa is commonly exposed to trauma. Von Bruns and Schrotter stated that the membranous glandular posterior wall is most frequently affected, either solely or simultaneously with one or both of the lateral walls, also relatively rich in glandular elements, while the cartilaginous anterior wall is usually spared, with the result that circumferential growths are rare. Fraenkel was in general agreement with these views.

As regards the histogenesis of these growths, von Langhans, Hamacher, Virchow and others expressed the belief that the origin is in the mucous glands. On the other hand, many authors have claimed cell enclavements and embryonal disturbances as etiologically significant. In support of the latter view, attention is called to the fact that the respiratory system develops from the anterior foregut.

For the occurrence of the squamous cell tumors and such mixed cell tumors as Hug's, we are rather inclined to the view of development from cell enclavements than to the theory of metaplasia, as enticing as the latter theory may appear. As concerns the histogenesis of the other types of carcinomas, we believe both theories tenable.

Tracheal carcinomas frequently metastasize not only in regional and distal lymph nodes, but in adjoining and distal regions. This is in contradistinction to the laryngeal carcinomas, which rarely metastasize, and which show a preponderance of metastases to a limited number of organs.

TUMORS WITH HISTOLOGY UNDETERMINED OR DOUBTFUL

We list thirteen tumors with undetermined or doubtful histology, making a total of twenty-seven on record. It is noteworthy that the present search revealed the largest number of unclassified tumors encountered by any reviewer—which is especially noteworthy in view of the fact that operative and microscopic methods have so greatly improved during the period covered by this review.

Only one of these tumors—that reported by Freudenthal—presented anything of interest. It occurred in a man 27 years old. On three occasions at yearly intervals tissue was removed through the laryngoscope. Finally, five years after the onset of symptoms, an open radical operation was performed, and the patient died. Histologically, the growth was variously called endothelioma, myxochondroma, cylindroma and finally, teratoma. We believe that there is a possibility of its having been a mixed tumor. Minnigerode's case, finally classified as a mixed tumor and Predescu-Rion's possible fibroma appear to us as better listed under this heading.

SUMMARY

An adenocarcinoma of the trachea is reported, with a review of tracheal tumors reported in the literature through the year 1929. The etiology, histogenesis and histology of the tumor types are discussed.

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CORRECTION

The following errors occurred in articles appearing in the March issue of the ARCHIVES OF PATHOLOGY

Avitaminosis I Pathologic Changes in Nursing and in Weaned Albino Rats Suffering from Vitamin B Deficiency Barnett Sure, Ph D, Fayetteville, Ark, Harvey S Thatcher, M D, Little Rock, Ark, and Dorothy J Walker, M S, Fayetteville, Ark

Page 414, line 13 "without" should read "with"

Page 422, last line of text matter, "second paper of this series" should read "this paper"

Avitaminosis II Pathologic Changes in the Albino Rat Suffering from Vitamin G Deficiency Harvey S Thatcher, M D, Little Rock, Ark, Barnett Sure, Ph D, and Dorothy J Walker, M S, Fayetteville, Ark

Page 425, seventh line from the bottom "Mandel" should read "Mendel"

General Review

BENZENE (BENZOL) POISONING

ALICE HAMILTON, M D

BOSTON

(Concluded from p 454)

CLINICAL OBSERVATIONS

Typical Form—In practically all of the articles on chronic benzene poisoning in man the famous cases described by Santesson and by Selling are quoted. These histories, therefore, are easily available to all readers, and so it seems better to substitute for them histories of more recent date or by authors less familiar and not so generally accessible.

Ronchetti's first case was in a girl, aged 18, who had been employed for three years in a raincoat factory. Her illness was, however, of only one month's duration, beginning with a severe nosebleed. She became very weak, suffering from repeated nosebleeds and abundant and prolonged menstrual flow. Then petechiae appeared, her throat became sore, and she was feverish. When examined, her tongue was dry, and there was a large scab on one tonsil, surrounded by a sub-mucous hemorrhagic area. Examinations of the abdomen and of the nervous system yielded negative results. Her red cell count was 1,000,000, white cell count, 800, hemoglobin, 27 per cent, color index, 1.35, and no platelets were to be seen. The red cells were normal, vital staining showing few reticulated cells. A differential count of the white cells showed polymorphonuclears, 26 per cent, lymphocytes, 70 per cent, large mononuclears, 2 per cent, eosinophils, 2 per cent. The clot formed in something over twenty minutes, but without retraction. The resistance to hemolysis was normal. Blood cultures were sterile. Cultures from the tonsils showed that *Staphylococcus aureus* predominated.

As the case developed, extensive retinal hemorrhage occurred in both eyes, and there was blood in the vomit. High fever, preceded always by a chill, delirium and coma developed, death occurred on the sixth day, with signs of pulmonary edema. The last examination of the blood showed that the red cell count had fallen to 795,000 and the hemoglobin to 15 per cent, the white cells were too few to count. At autopsy the spleen was small, the pulp was scanty, the trabeculae were increased, there were no follicles. The liver was anemic, the kidneys contained small hemorrhages, and there was a hemorrhagic focus in the ovary. The femoral marrow was scanty and retracted, so that the cavity appeared half empty, it was yellow with a few red points, and under the microscope there were noted an absence of youthful white elements, very few polymorphonuclear cells and still fewer megakaryocytes, but many nucleated red cells, typical normoblasts and normal red cells.

Cremieu's case occurred in a man, aged 25, who eight days before had been in good health. At that time he noticed for the first time purple spots on his chest and suffered from slight headache and feverishness. He was a vigorous man, who had gone through the War without any serious impairment of health. For six weeks before his illness he had been employed in producing pyramidon, using benzene as a drying agent. The man who had filled this place before him had left because of repeated nosebleeds. The process liberated fumes of benzene, but still worse was the work of cleaning the apparatus, which took fifteen minutes four times a day and was done with benzene. When he entered the hospital he was suffering from uncontrollable nosebleed and extreme anemia, and was apparently moribund. The nosebleed had lasted twelve hours. There were also bleeding from the gums and a gangrenous patch on the lining of the lower lip. The temperature was 40 C (104 F). There was loss of vision for several hours from a bilateral retinal hemorrhage. The red cell count was 1,200,000, later 900,000, the white cell count was 600, later 1,200. At the second count, after four transfusions, the hemoglobin was 18 per cent, the index was normal. There were no abnormal red cells. The differential count gave polymorphonuclears, 27 per cent, lymphocytes, 65 per cent, large mononuclears, 3 per cent, medium, 5 per cent. The patient died after the fifth transfusion, conscious till death. The autopsy revealed nothing significant, except hemorrhages. The marrow of the sternum was apparently normal, the liver showed areas of fatty degeneration.

The case described by Lande and Kalinowky occurred in a man, aged 26, who worked in a factory using lacquer with 40 per cent benzene. The lacquer trickled on paper which passed along a traveling belt, and the man sprinkled bronze powder on it to make gilt paper for the ends of cigarettes. He suffered first from loss of appetite, increasing gastric disturbance and weakness, then bleeding from the gums and from the nose began, and purpuric spots appeared on the skin. The loss of blood increased, and he became very weak. An uncontrollable attack of bleeding from the nose sent him to the hospital, where his temperature was found to be 40 C (104 F), but there was no other notable physical symptom. The red cell count was 1,000,000, the hemoglobin, 35 per cent, the white cell count, 2,000, with 76 per cent lymphocytes. There were no nucleated red cells, but there was a marked variation in the size, shape and coloring of the red cells. The platelets numbered 34,000, the bleeding time was more than fifteen minutes, the clot formed in four and a half minutes. The blood culture was negative. The patient died after eight days, the hemorrhage being uncontrollable all the time. His mind was clear till two hours before death.

Autopsy showed no signs of sepsis or of leukemia. There were extensive hemorrhages in the mucous membranes of the mouth, nose, bronchi, stomach, and urinary bladder and in the epicardium, endocardium, pelvis of the kidney, and the pia mater. The marrow was aplastic, the spleen, small and anemic. There was a striking degree of fatty degeneration of the endothelium of the blood vessels in the liver and kidneys. The authors commented on the fact that the loss of platelets was greater than that of red blood corpuscles. The extravascular clotting time was normal, as in the essential thrombopenia of Werlhof, showing a disturbance in the clotting mechanism of the blood vessels. Most of the symptoms were attributable to this disturbance, which is due to an injury to the epithelium of the vessels. The high septic temperature they explained as caused by the absorption of products of decomposition of the cells.

The case described by Laignel-Levastine, Levy and Desoille, was in a woman, aged 19, who had worked for six months in a raincoat factory using "benzine"⁸ February 1 she went to a dentist because of pain in the right side of her mouth. He found ulcers and hemorrhage in the mucous membrane of the mouth. A little later purpuric spots developed on the skin and bleeding from the uterus. Bleeding from the gums became uncontrollable. The patient then went to the hospital, where it was found that she showed extreme pallor, a temperature of 39.5 C (103.1 F), a pulse rate of 118, a respiration rate of 24, bleeding from the nose, mouth and uterus, a few purpuric spots on the skin and exaggerated reflexes. The bleeding time was three minutes and a half, the clot formed in seventeen minutes, with no retraction. The red cells numbered 2,120,000, the hemoglobin was 40 per cent, the white cell count was 1,200, with polymorphonuclears 32 per cent, small mononuclears 16 per cent, medium mononuclears 50 per cent and large mononuclears 2 per cent. There were no abnormal red cells, the blood culture was negative, the platelets were much diminished. Later the red cells fell to 806,000, hemoglobin to 18 per cent and leukocytes to 700. Transfusion was followed by temporary improvement, but three days later hemorrhage recurred. Two days before death the patient became delirious, her temperature reached 40.8 C (105.4 F), the pulse rate was 140, the respiration rate, 50. Only 77 leukocytes were found in 8 smears, 65 of them mononuclears and 12 polymorphonuclears. Most of these cells were normal, with clear cytoplasm. Some had azure grains, and a few had somewhat atypical nuclei, but they were not lymphoblasts. The patient died on the twelfth day after entering the hospital, the red blood cells numbering then only 700,000.

Rohner, Baldridge and Hausman reported an interesting case of fatal benzene poisoning in a man, aged 32, who mixed the coating dough in a can factory, using benzene as a solvent. He quit the work after about ten weeks because the fumes irritated his eyes, but about a month later, with no further exposures to benzene, blood appeared in the stools and hemorrhagic spots in the skin, later blood blisters formed in the lining of the mouth, and the gums became sore and black. A nose-bleed lasting three days sent him to the hospital on May 27. Two days before, a shower of red spots had appeared over the legs and thighs. He fainted on his way to the hospital. The skin was pale, not yellow as in hemolytic anemia, and the spleen was not palpable. The red blood cells numbered only 860,000, with marked anisocytosis, poikilocytosis and achromia and with no macrocytes and no nucleated red cells. The white cell count was 1,400, of which 13 per cent were polymorphonuclears, 48 per cent lymphocytes and 39 per cent endothelial leukocytes. The hemoglobin was 20 per cent, the platelets numbered 70,000. The bleeding time was thirty minutes, the prothrombin time, sixteen minutes. The clot formed in thirty minutes, but there was no retraction after twelve hours. On May 30, after transfusion, the axillary temperature was 108.2 F, the pulse rate was 164 and the respiration rate was 34, with chills, bloody vomitus and pain in the left ear. Paracentesis allowed bloody fluid to escape, and the bleeding continued for thirty minutes. Two transfusions were given and four intramuscular injections of blood. On June 3 a blood culture was made, but was negative. Drowsiness and delirium were present during the last week before death, and the red blood cells fell to 720,000, with 16 per cent hemoglobin.

These are typical histories of chronic benzene poisoning, but variations from the type are not infrequent and also variations from the

⁸ This is the word used very often by the French, but in some cases it is plain that benzene is meant.

typical blood picture Following is a summary of the results of examination of the blood in eighty-five cases

Observations on the Blood—The blood picture in benzene poisoning of human beings does not follow the pattern which has been established by many experimenters as characteristic of experimental poisoning in animals As described in foregoing paragraphs, benzene when administered to animals either by injection or by inhalation produces a marked granular leukopenia, but little diminution of the red cells,⁹ often none at all In benzene poisoning in man, on the other hand, profound anemia, aplastic in type, is characteristic, and this may be more striking than the leukopenia

Typical blood pictures in cases of chronic benzene poisoning as it occurs in industry are as follows

In Hunter and Hanflig's fourth case there were 1,715,000 red cells The hemoglobin was 40 per cent, the white cells numbered 1,200, and consisted of polymorphonuclears, 16 per cent, lymphocytes, 76 per cent, and large mononuclears, 8 per cent The platelets were rare There were moderate achromia and variation in the size of the red cells The bleeding time was ten minutes, and the clot formed after nineteen minutes Cabot's case of fatal poisoning (no 13391) showed marked leukopenia, with a white cell count of 400 and in two smears an absence of polymorphonuclears, while in the third they constituted only 1 per cent The red cell count was 1,715,000, the red cells were normal, with no reticulated cells, the hemoglobin was 40 per cent Platelets were practically absent, the bleeding time was sixteen minutes, the clot forming in from twelve to nineteen minutes In the case reported by Rivet and Guédé, also ending in death, the red cell count was 1,520,000, the hemoglobin, 45 per cent The white cell count was 1,800 Polymorphonuclears made up 42 per cent of the white cell count, mononuclears 54 per cent and eosinophils 4 per cent, but the mononuclears were almost all medium-sized, with a few large, and still fewer small, lymphocytes There were no myelocytes or normoblasts The platelets numbered 41,000, the bleeding time was eleven minutes, and the clot formed in twenty-one minutes, but with no retraction

Askey's second patient had anemia more striking than the leukopenia The red cell count was 1,200,000, with hemoglobin 29 per cent, the white cells numbered 3,300, with 67 per cent lymphocytes, the platelets numbered 50,000, the bleeding time was twenty-six minutes There was no abnormality of size, shape or staining in the red cells

Red cell counts under 1,000,000 do not often occur, but have been found in fifteen of the seventy cases in the reports of which counts are given (Lagnel-Levastine Rohner, Baldrige and Hausman,

⁹ See, however, Weiskotten, p 31

Flandin and Roberti, Cremieu, Meda, Martland [first and third cases],¹⁰ Smith [case 33, reported in 1928], Selling [first case reported in 1910], Batehelo [eleventh case], Santesson [third case], Hogan and Schiader [second and third cases], Ronchetti [two cases]) In thirty-five cases it fell to a point between 1,000,000 and 2,000,000, in eleven, to between 2,000,000 and 3,000,000, in six, to between 3,000,000 and 4,000,000, and in three, it was over 4,000,000 This does not mean that other counts in cases in which repeated examinations of the blood were made did not show a higher number of red cells The statement concerns the lowest counts in each case

Typically, the red blood cells are unchanged, or show no abnormality beyond some variation of staining, shape and size There are, however, some exceptions to this rule The variations in size and shape may be rather striking, as in Hunter and Hanflig's second case and in their sixth case, in the case of Lande and Kalinowsky, in the case of Faure-Beaulieu and Lévy-Bruhl (1922), in the second case of Anderson Boyd and Jackson and in Martland's fourth case Paul and his associates noted basophil cells Normoblasts, few in number, were seen by Weinstein,¹¹ by Hunter and Hanflig in their third and sixth cases by Ronchetti in his second case, in which there were four nucleated red cells per hundred leukocytes, and by Oettinger, who found as many as six Fewer reticulocytes than normal were seen by Ronchetti, when he used vital staining Hunter and Hanflig estimated the proportion of reticulocytes as 1.5 per cent in their first case, and as from 1.6 to 3.2 per cent in the second case These cells increase in number as improvement comes on (Hunter and Hanflig, Smith)

Platelets are mentioned in forty-four reports, but only in fourteen is a count given, the lowest count which is in Selling's second case, was 2,500, the highest in Askey's first case was 100,000 Usually the statement is made that the platelets are "much reduced," "rare," "almost absent," "none seen," "practically none"

The bleeding time is given in only twenty reports, and runs from four and one-half minutes (Hunter and Hanflig's sixth case) to more than half an hour (Smith Hunter and Hanflig) The time taken for a clot to form is given in sixteen reports This is from four and one-half minutes (Lande and Kalinowsky) to two hours (Faure-Beaulieu and Lévy-Bruhl) The clot may fail to retract even after a long period (Selling, twenty-four hours, Rohner and his co-workers, twelve hours, Askey, seventy-two hours)

¹⁰ Dr H S Martland, Chief Medical Examiner of Essex County, N J, let me quote histories of one case of acute and ten cases of chronic benzene poisoning, all fatal, which came to his knowledge between 1924 and 1929

¹¹ Personal communication to the author

The hemoglobin is always reduced, usually to a low figure, less than 10 per cent in Selling's first case, and less than 20 per cent in his second and in Martland's third, Hogan and Schrader's second and third, Ronchetti's second and the cases of Flandin and Roberti, Ciémieu, Rohner and his associates, Laignel-Levastine, Lévy and Desoille, Newton and Meda and in Smith's case 33. In the great majority it is between 25 per cent and 55 per cent. A hemoglobin content of more than 55 per cent is decidedly rare (see Hunter and Hanflig's first case).

The color index is said to be characteristically low in benzene poisoning. Cabot (1904) said that the color index is rarely high in any disease of the blood, except pernicious anemia. Faure-Beaulieu and Lévy-Bruhl (1924), however, said that the index is typically high in benzene poisoning. Tabulation of the data given with regard to seventy-seven cases does not confirm either statement. In seventeen the index is low, between 0.55 and 0.85, in 22 it is high, between 1.3 and 2.3, and in 38 it is normal, between 0.9 and 1.2. In the majority of cases, therefore, it falls between normal limits, but in a slightly larger number it is abnormally high rather than abnormally low. An index as low as 0.6 was found in Selling's three cases, Hogan and Schrader's second case and Legge's first. The highest indexes are in one of mine, with 2.3, Smith's case 33, with 2.1, Hunter and Hanflig's first, with 1.8, and in the cases of Hogan,¹² Landé and Kalinowsky, Smith (case 28) and in one of mine, with 1.7 each.

Smith's statement that the index is higher in cases with pronounced anemia is confirmed by these cases. Of the twenty-two with high indexes, seventeen had red cell counts below 2,000,000. In Smith's case 33, early in the history, there was a count of 2,240,000 and an index of 0.79, but later, when the count fell to 480,000, the index rose to 2.1. In Batchelor's eleventh case there was an index of 1.35 when the red count was 1,055,000, but when the count was doubled, the index was only 0.75.

On the other hand, in mild cases with a fairly normal red count, the index is likely to be low. For instance, in Batchelor's sixth case there was a high count, 5,424,000, with an index of 0.6. It is true that in Selling's two cases the counts and indexes were low.

Ronchetti found the resistance to hemolysis normal in both his cases yet he believed that in the second one there must have been a rapid destruction of red blood corpuscles, because of the intense urobilinuria (see page 71). Hunter and Hanflig tested the fragility of the red cells in their first cases and found it normal, and Meda found the same. Faure-Beaulieu and Lévy-Bruhl, however, said that the globular resistance is increased in benzene poisoning.

¹² Personal communication to the author.

The white cell count is given in eighty-five cases. Taking the lowest count in each instance I find that in eleven it is 600 or lower, in seven between 600 and 1,000, in twenty, over 1,000 and under 2,000, in twenty-one, over 2,000 and under 3,000, in ten, from 3,000 to 4,000, in seven, over 4,000 and under 5,000, and in nine, over 5,000. Very pronounced leukopenia without actual count, was noted by Santesson in his fourth case, and Ronchetti said that his first patient just before death had too few white cells to count. Laignel-Levastine, Levy and Desoille could find only seventy-seven in eight smears.

High counts were found in a few instances. In Harrington's second case the first count was 10,000, falling later to 750. Nothing is given in the history to explain this, no infectious process was noted. In the case described by Paul, Friedlander and McCord, the count was 24,000, but here suppuration was known to be present, and this was true also in Meda's case, in which the count rose to 7,000.

A differential count of leukocytes was made in fifty-six cases only. In the majority it showed a granular leukopenia,¹³ the polymorphonuclears in forty-two cases ranging from 2 per cent to 50 per cent. The polymorphonuclears formed less than 30 per cent of the white cells in fifteen of these forty-two cases. Only in fourteen cases was a normal proportion of polymorphonuclears (from 50 per cent to 70 per cent) found, except in the later stages of recovery. The patient of Paul, Friedlander and McCord was septic and 71.9 per cent of the white cells were polymorphonuclears. A similar cause, namely, Vincent's infection of the mouth, probably explains the initial count in Hunter and Hanflig's fourth case, which was 5,800 white cells, with 82 per cent polymorphonuclears, but which fell promptly to 1,200, with only 16 per cent polymorphonuclears.

The most marked degree of mononucleosis is found (1) in the case (13391) reported by Cabot in which there were no polymorphonuclears in two smears and 1 per cent in a third, and (2) in that of Flandin and Roberti, in which only 2 per cent of the white cells were polymorphonuclears. The small mononuclears made up 59 per cent, the medium-sized 27 per cent and the large 12 per cent. Next to this comes the mononucleosis in the case of Speidel and Melgard, with 4 per cent polymorphonuclears. In Askey's first case 90 per cent of the leukocytes were mononuclears. In several instances the granular leukopenia

¹³ Selma Maver working in Schlossmann's clinical laboratory in Dusseldorf found that lymphocytosis with reversal of the normal leukocytic formula is characteristic of the action not only of benzene, but of toluene, xylene, anthracene, aromatic nitro compounds, arsine, thallium and hydrocyanic acid and she suggested that the cause is to be sought in functional disturbances in the endocrine glands. These studies were all made on human beings (*Changes in the Blood as Reflecting Industrial Damage*, J. Indust. Hyg. **10** 29, 1928).

improved with the recovery of the patient, as in Hunter and Hanflig's first and second cases, Brucken's first and Hogan and Schrader's third and in Smith's case treated with fresh liver (1929), while it became aggravated with intensification of the disease in Hunter and Hanflig's fourth and sixth cases, in Askey's second and in Maitland's eleventh.

Too much trust should not, however, be placed in the differential count alone, for mononucleosis may be slight or absent even if there is no evidence of suppuration. Thus in Maitland's seventh case, which was one of fatal poisoning, polymorphonuclears were 60, lymphocytes 25, large mononuclears 8, and eosinophils 5, per cent. In Hunter and Hanflig's fifth and sixth cases, both fatal, the polymorphonuclears were 60 and 64 per cent. In Batchelor's eleventh case the smear showed a fairly normal picture, 58 per cent polymorphonuclears, 36 per cent lymphocytes and 5 per cent large mononuclears, but the count revealed only 1,055,000 red cells and only 1,450 white cells. A serious mistake might have been made here had only the smear been examined.

The mononuclear leukocytes are usually described as predominately lymphocytes, or small mononuclears, but in some cases the large predominate. Thus in the case of Laignel-Levastine Levy and Desoille, 85 per cent of the mononuclear cells were large. In Oettinger's second case, in the case of Faure-Beaulieu and Lévy-Bühl, in one of Smith's, in Rivet and Guede's and in Newton's, the large and medium-sized exceeded the smaller mononuclears. Rohner and his colleagues found endothelial cells making up 39 per cent of all the leukocytes. Chambonet's fourth patient had 36 per cent mononuclears, only 6 per cent of which were small.

The highest proportion of small mononuclears is found in Speidel and Melgard's case, with 84 per cent, in Askey's two cases, with 90 per cent and 72 per cent, in Ronchetti's first case, with 70 per cent, in Hunter and Hanflig's fourth, with 76 per cent, and in Selling's second, with 71 per cent.

Young polymorphonuclears, with two-lobed nuclei, were noted by Hunter and Hanflig in three cases, and they saw also other immature forms. The blood picture in the third case was reported as follows: polymorphonuclears, 22, small lymphocytes, 16, large lymphocytes, 14, large mononuclears, 10, eosinophils, 2, atypical cells with nucleoli (possibly immature bone marrow cells or myeloblasts), 22, large similar cells, 10, immature myelocytes, 2, typical myeloblasts, 2. In the second case, atypical lymphocytes made up 9, and atypical large mononuclears 17 per cent. "Unclassified large mononuclears" were noted by them in several cases. Martland found myelocytes making up 6 per cent of the leukocytes in the blood of his eleventh patient. In the blood of a patient treated in the Johns Hopkins Hospital in

1918, the white cells were 39 per cent polymorphonuclears, 36 per cent lymphocytes, 8 per cent eosinophils¹⁴ and 16 per cent large mononuclears with marked azurophil granulations

In experimental poisoning the leukopenia is always far in excess of the anemia in human poisoning the reverse is often found. This is true of no less than twenty-two of the seventy-five cases in which both red cell and white cell counts were made. Thus in two of Batchelor's cases the counts ran as follows: red cells, 1,736,000, and white cells, 4,200 in the first; red cells, 800,000, and white cells, 3,000, in the second. In Smith's "case 33" the count was 3,800 white cells and 480,000 red cells. In Askey's second case there were 3,300 white cells to 1,200,000 red cells, in Hunter and Hanflig's second case there were 3,000 white cells to 1,700,000 red cells, in Maitland's tenth case at death there were 4,200 white cells to 1,300,000 red cells, with an index of 1.6, and in Bruckens's first case there were 6,833 white cells to 1,515,000 red cells. In the relapse in Hunter's first case there were only 1,900,000 red cells, but the white count was normal, 7,000, although the differential count showed a granular leukopenia of 33 per cent. These cases do not include those in which the white count was obviously affected by an infectious process, they are discussed separately.

In some instances the same case will show at one examination a disproportionately low white cell count and at another a disproportionately low red cell count. In Hunter and Hanflig's third case the anemia was at first more pronounced than the leukopenia (3,000 white cells, 1,700,000 red cells), but later the reverse was true (340 white cells, 2,550,000 red cells). The number of cases in this series with leukopenia greatly in excess of anemia is smaller than the number with anemia as the most striking feature, namely seventeen of the former and twenty-two of the latter.

The blood changes in early benzene poisoning or in mild cases of poisoning (it is impossible to distinguish between the two) often resemble those in experimental poisoning more closely than do the changes in pronounced cases. The red cell count is likely to be less affected than the white (see Batchelor), the color index low and the differential white count deviating from the normal more than the absolute count. Batchelor's sixth case is one in point. Here there was a high red cell count, 5,424,000, with only 70 per cent hemoglobin, the white cell count was 6,140, a little more than half of them mononuclears. In Newton's first case there were 5,760,000 red cells, a color index of 0.7, and only 1,200 white cells, of which 39 per cent were large mononuclears.

14 For eosinophilia, see page 50

It is in just this form of poisoning that one might expect to see evidence of the stimulating action of benzene on the marrow such as has been described by experimenters, but there are few such observations dealing with human beings. This is probably explained by the small number of careful examinations that have been made on people exposed to benzene, but not yet actually poisoned. A few reports of examinations of groups of men and women working with benzene have been published, such as those by Teleky and Weiner and by Floret (1927) in Germany, by Loewy in Prague, by Heim, Agasse-Lafont and Feil (1924) in France and, in this country, by Batchelor, working with the Benzene Committee of the National Safety Council, by Smith, then of the New York State Department of Labor, and by Paul, Friedlander and McCoid.

Floret seems to have found his subjects actually in the stage of marrow stimulation, according to a rather extraordinary observation which he made during the war. He examined a group of women working with benzene who presented an appearance of blooming health in spite of the great scarcity of food in Germany at that time. These women were a decided contrast to the other women workers, who were all pallid and undernourished. Their blood had a high hemoglobin content and an abnormally high white cell count. In spite of close observation Floret could detect no injury from the benzene. Unfortunately the description of the observations on the blood is far from complete, and one cannot say whether there was an actual polycythemia such as was described by Langlois and Desbouis as occurring in animals.

Loewy also found leukocytosis in benzene workers. He had the opportunity to follow mild attacks of benzene poisoning in a group of makers of artificial flowers. These attacks consisted in a slight rise of temperature, to 38.1 C (100.6 F), and leukocytosis up to 16,000 white cells, 80 per cent of them polymorphonuclears, which passed over in a few hours.

Teleky and Weiner found some evidence of activity of the marrow in a small proportion (three of eleven in one plant) of the nineteen women and eight men whom they examined, such as nucleated red cells and polychromatophilia. Almost all showed anisocytosis and poikilocytosis. They found lymphocytosis in almost all, and they regarded this as the best evidence of early poisoning. They did not find eosinophilia. Heim, Agasse-Lafont and Feil found a tendency to polynucleosis, i. e. a proportion of over 70 per cent in ten of thirty persons and of less than 60 per cent in only five. They found eosinophilia (over 5 per cent) in nine persons and are inclined to add to them five more who had 3 per cent eosinophils. In an earlier article (1912)

they asserted that eosinophilia was present in 80 per cent of the workers with benzene who were examined, that it appears early, disappears soon if exposure ceases, and bears no relation to the intensity of the clinical symptoms. But obviously the number of eosinophil cells which they regard as abnormal is far too low.

Chambovet agreed with these French observers as to the frequency of eosinophilia in workers exposed to benzene, and three of his cases, all fairly mild, showed a high count, 7 per cent, 14 per cent and 7 per cent, the last with an additional 6 per cent of eosinophil myelocytes. These cases showed other evidences of irritability of the marrow, namely, poikilocytosis and numerous young red cells, with some macrocytes. Simonin, in a case of acute benzene intoxication, with fever, bronchial catarrh and eruptions in the skin, found a decided eosinophilia of 25 per cent on the fifth day, dropping to 2.5 on the thirteenth. Calamita also believed that eosinophilia is typical of the blood in benzene poisoning.

Batchelor, acting for the Benzene Committee of the National Safety Council examined eighty-one workers exposed to benzene and found twenty-six suffering from poisoning. In these cases the white cell count was reduced more strikingly than the red cell count, the lowest normal count of white cells being taken as 5,600. The blood counts in thirteen cases are given in detail, among these cases were four showing very severe anemia, but the other nine may be considered mild cases. These had the low color index characteristic of mild poisoning—for example, 5,400,000 red cells with a color index of 0.64, the mononucleosis was not over 50 per cent, and in two of them there was eosinophilia, 7 per cent and 8 per cent.

Smith examined seventy-nine women engaged in work with benzene, among whom she discovered from twenty-five to thirty with mild poisoning. The index was low in 22 per cent, and there was a tendency to mononucleosis even when the count was normal. Three women showed some increase of red cells, over 5,000,000, which in factory women is excessive. An abnormal proportion of eosinophils was noted in only two of the cases, namely 8 per cent in one and 13 per cent in the other. She also noted an increase in the endotheliocytes, or large mononuclears and transitionals. In fifteen of twenty-eight examinations she found an increase above 6 per cent, in one to 19 per cent. In another case they numbered 27 per cent and in still another 11 per cent. There was also a slight increase in mast cells in nine women (to 1 per cent or 2 per cent). Three of these women had clinical symptoms of benzene poisoning, but no leukopenia (the white cells were over 6,000) and not more than mild anemia nor were the polymorphonuclear white cells reduced below 52 per cent.

Paul, Friedlander and McCord called attention to a feature in the blood in early benzene poisoning which they believed to be much more trustworthy than leukopenia. This is an increase in basophil red cells. The routine white cell count may fail to give warning, for in severe cases of benzene poisoning there may be normal or even overnumerous white cells, while in exposure to low concentrations of benzene and in the early stages of exposure to high concentrations the mutant effect of the poison is shown in the presence of immature red cells, those containing basophil substances. They found an excess of basophil erythrocytes in experimental animals—cats, rabbits and guinea-pigs.

They examined the blood of eight women who were using a benzene spray and found seven with polychromatophilia and nucleated red cells. A man who suffered from acute poisoning, with loss of consciousness, followed by severe bronchitis with inflammation of all the accessory nasal sinuses, had no leukopenia, but the basophil red cells were greatly increased. In another workman, a painter, with chronic poisoning, the red cells were reduced to 3,370,000, but the white cells numbered 24,000, with 71.2 per cent polymorphonuclears, which would not point to a diagnosis of benzene poisoning. The leukocytosis, however, was explained by chronic bronchitis, and the red cells were characteristic, showing a high proportion of basophil elements, 11,000 per cubic millimeters. They pointed to the fact that when benzene is used in therapeutics its use is often followed by a marked leukotoxic action associated with an increase in red blood cells.

Unusual Features—There are certain features of the clinical picture of benzene poisoning as it is described by various observers which deserve special attention.

Retinal hemorrhage is mentioned ten times in Ronchetti's two cases, Ciemeu's case, Oettinger's second case, Hunter and Hanflig's third, Askey's second, Selling's second, Speidel and Melgard's case, Loewy's case, and the Johns Hopkins case. Ronchetti believed that the number is so small because an ophthalmoscopic examination is rarely made, for retinal hemorrhage is really a typical symptom of benzene poisoning. Cabot in "Diseases of the Blood" gave the same reason for the small proportion of American cases of pernicious anemia in which this symptom is noted as compared with the number of foreign cases.

The absence of platelets or their marked diminution, is one of the typical features of the blood in benzene poisoning and hemorrhage from mucous membranes, into the subcutaneous tissues and into serous membranes and organs is one of the cardinal symptoms. Yet there are cases on record in which no hemorrhage was noted during life. Hunter and Hanflig's seventh case occurred in a man who worked with benzene and who had a leukopenia of 1100 falling to 550 before death, with

only 16 per cent polymorphonuclears, and a red cell count of 1,125,000. The platelets underwent a progressive decrease, but clinically purpura did not appear. Then sixth patient, a woman with milder poisoning ending in recovery, had apparently no history of bleeding, except a profuse menstrual period, yet here also the platelets were markedly diminished.

In Oettinger's second case hemorrhage occurred in the retina only. Genova spoke only of metrorrhagia, in his two cases, and both of these were in pregnant women. Hogan and Schrader's second case occurred in a pregnant woman, and here hemorrhage from the uterus with abortion is the only symptom given.

In Martland's ninth case there was no purpura, and benzene poisoning was not suspected because of the marked buccal sepsis. The man was supposed to have died of osteomyelitis of the jaw, but at autopsy Martland found aplastic marrow, leukopenia and anemia with no regeneration, and since the man was exposed to benzene in a plant in which several other cases of benzene poisoning had occurred, Martland made the diagnosis of benzene intoxication. His tenth case was another without hemorrhage, for although there was slight bleeding from the gums, this could be accounted for by the foul condition of the mouth, with spongy gums and dirty, carious teeth. There was no evidence of old or fresh hemorrhage in the skin. His third case was diagnosed clinically as Vincent's angina with anemia. At autopsy, irregular, small purplish areas of hemorrhage were found in the mouth, in which sepsis was marked but none in the skin, and no hemorrhage had occurred during life. The blood picture, however, showed typical benzene poisoning.

Pregnancy complicated the course of the disease in Santesson's ninth case, in Hogan and Schrader's second case, in one of Smith's, in Meda's and in Rivet and Guéde's, in the last there was also a tendency to hemophilia from childhood. One of the cases reported to me by an industrial insurance company was that of a pregnant woman suffering from benzene poisoning who died of "uremic convulsions." Smith's "case 28" was that of a woman who had never suffered from the benzene until she became pregnant, then severe and prolonged attacks of nosebleed began, followed by bleeding from the gums and the rectum and under the skin. She stopped work for a while and improved, but when she went back to work the purpura recurred, she miscarried at seven months, and died of postpartum hemorrhage. Hogan and Schrader's patient, who also died of postpartum hemorrhage after being delivered of a macerated fetus was supposed to have a placenta praevia.

Among the rarer symptoms described in these histories are nervous symptoms other than the usual headache, dizziness, delirium and coma.

hemorrhage into the middle ear or into the internal ear, and bleeding from the kidneys, polyuria and nocturia. Pugliese said that he had seen patients with polyneuritis and sometimes with retrobulbar neuritis. Two of Chambovet's patients had marked paresthesias, and Faure-Beaulieu and Levy-Bruhl's patient had symptoms pointing to lesions in the pyramidal and sensory tracts of the cord. Martland's eleventh patient, in whom benzene poisoning was considered questionable, had the paresthesias which are associated with pernicious anemia. Wyss, quoted by Genhard, reported a case in which there was obstinate dizziness so severe as to make standing up impossible, together with disturbed sleep, bad dreams and psychic depression. Lande and Kalinowsky's second patient had toxic neuritis of the arms affecting the median nerve with laming of the muscles supplied by it, loss of faradic and galvanic irritability and marked vasomotor-trophic disturbances. Disturbances of the skin other than hemorrhage are fairly common in workers with benzene (see McCord, Pugliese, Starr), and are usually attributed to the dryness of the skin, followed by cracking, caused by the solvent action of benzene on the oil of the skin. This explanation was given by Lande and Kalinowsky, but Floret expressed the belief that benzene is in part excreted by the skin and does its damage in this way.

The fact that the action of benzene continues after its administration has ceased has been observed in experiments on animals, and is one reason for the abandonment of the therapeutic use of benzene (see Koriany). This action is repeatedly illustrated in the clinical histories especially those of severe poisoning. In Selling's first girl patient, all the serious symptoms developed after she had left work. Four of nine of Santesson's girl patients had purpura only after they had left the factory. His first case occurred in a girl, formerly vigorous, who quit work simply because she was growing pale and weak. Later purpuric spots appeared, scorbutic ulcers in the mouth, fever and increasing weakness, with sudden death from heart failure. The case described by Rohner and his colleagues had a somewhat similar history. A man had worked with benzene for ten weeks, then he quit because the fumes irritated his eyes, not till a month later did hemorrhages begin, and then the disease progressed to fatal aplastic anemia and purpura hemorrhagica. In a large number of cases the blood picture undergoes rapid change for the worse after the patient has reached the hospital. An exposure of many years, followed by a sudden development of severe poisoning is the history given in Loewy's case, in Faure-Beaulieu and Levy-Bruhl's case and in Martland's second case.

A very rapid course of the disease is described by several authors. Cremieu's patient died eight days after the onset of the symptoms. Hogan and Schrader's first patient had worked only six weeks. She

began to feel ill on March 4, had her first hemorrhage on March 10, went to the hospital on March 14 and died on March 19. The history of Martland's fourth case shows that the patient went to the hospital for a severe nosebleed and died five days later. His seventh patient worked only three months, then had bleeding from the mouth and nose and purpura and died after five days. Hogan and Schrader's patient, a girl, was employed for only one month in a well ventilated can factory. Fifty other women working in the same room, some of them for several years, had no symptoms of poisoning, but this girl died ten days after the onset of hemorrhage from nose, mouth, uterus and rectum.

A varying susceptibility to benzene poisoning was noted by many experimenters on animals (see, for instance, Simonds and Jones, Hektoen, Selling) and is strikingly illustrated in industrial cases, the victims of which always constitute a small minority of the workers, in many cases—as in the one just cited—a single individual may contract fatal poisoning in an environment that does not give rise even to mild poisoning in the others. Rivet and Guede, Ronchetti and Meda all emphasized this fact. Pugliese found that repeated inhalations causes sensitization in some animals, but Teleky and Weiner from their observations on human beings, thought that prolonged exposure may lead to increased resistance to the poison. Practically all the Italian and French writers (see Zenoni and Delaue), emphasized the susceptibility of women, especially of young women, and this seems to be borne out by the experience of American industrial insurance companies, but Smith, who examined seventy-nine women exposed to benzene in their work, did not find the younger women the most susceptible—rather the contrary. She discovered twenty-five, perhaps thirty, cases of chronic poisoning in these women, but the highest proportion was in the older groups. Thus there were but two of seventeen girls under 20 years of age, or 11.8 per cent, who were poisoned, while among the thirty-four women between 20 and 30 years of age there were sixteen, or 47 per cent, and among the twenty-eight who were over 30 years of age, 12, or 42 per cent. She believed that when susceptibility exists, the evidence of poisoning is likely to come to light during the first year, in some, during the first three months. Teleky and Weiner thought that there is no proof of oversusceptibility in women. Calamita found young men more vulnerable than older men.

Recovery—There are a few cases recorded in which clinical recovery occurred after severe intoxication, although in almost no instance did the final examination show normal blood. Recovery when it occurred, was typically slow and incomplete, which means either that the hemopoietic tissues had suffered irreparable damage or that no case was

followed for a long enough period. A typical instance was reported to me from an electric wire insulating plant. The man had on admission to the hospital a red cell count of only 800,000, with hemoglobin 23 per cent. The leukopenia was less marked, 3,000 white cells, 40 per cent of them polymorphonuclears. He was given three transfusions and was under treatment in the hospital for fifty-seven days, but at his discharge, although subjectively he was much improved and was free from hemorrhage the red cell count was only 2,112,000, with hemoglobin 40 per cent, and the white cell count was 1,800, with 47 per cent polymorphonuclears, and the only evidence of activity of the marrow was a moderate amount of polychromatophilia and variation in the size and shape of the red cells.

It should be noted in this connection that Weiskotten and his colleagues (1920) found in their experiments with benzene administered to rabbits through inhalation, that recovery was greatly delayed or incomplete as shown by leukopenia persisting even after from 368 to 458 days.

Hunter and Hanflig remarked that in two patients of theirs who recovered, the white cells never fell as low as 1,000, while in the two who died from benzene poisoning, the white cells fell below that. However, Hogan and Schrader's third patient had a count of 950 and yet recovered. This was an unusual instance of severe poisoning, with rapid improvement, the red cells rising in one week's time from 880,000 to 2,184,000, the white cells, from 950 to 3,050.

Two instances of recovery under liver therapy were reported although only one was published. This was Smith's case (1929), that of a man who came to the hospital with uncontrollable bleeding following the extraction of a tooth. The red cell count was 2,820,000 hemoglobin 56 per cent, the white cell count was 1,300, with 75 per cent mononuclears, the platelets numbered 25,000, with a bleeding time of thirty-three minutes. At discharge the red cell count had gone up to 3,780,000 and the white cell count to 5,800, with only 40 per cent mononuclears. Reticulocytes were fairly abundant among the red cells at this stage 86 per cent but not as conspicuous as in pernicious anemia under liver therapy. The other case in which liver therapy was successful came to me from an insurance company.

A man worked with benzene in manufacturing artificial leather, and went to the hospital after four months because of bleeding from the gums, the nose and the sockets of extracted teeth and because of blotches and petechiae practically all over the body. Only the white cell count is reported—2,000. Three transfusions were given and the patient was put on a diet of half a pound of liver daily. Bleeding stopped a month later the white cell count improved, and the patient was discharged after two months' further treatment. The last white cell count is given as 4,700.

The best record that I have of return to a normal blood picture after benzene poisoning is one sent me by Dr J H Weinstein of Terre Haute, Ind., who followed the case with unusual perseverance, so that he could present blood counts covering the period between Dec 2, 1926, and Nov 10, 1927

A woman employed in a cleansing and dyeing establishment was seen at an early stage of the poisoning, when the results of physical examination were practically negative. The symptoms were of a functional nervous character only, and the blood count was red cells, 4,200,000, normal in appearance, hemoglobin, 80 per cent, white cells, 6,600, with normal differential proportions. About three weeks later the red cells had fallen to 1,100,000 and the white cells to 2,400, the smears showed anisocytosis and poikilocytosis, a few nucleated reds and very few platelets. The patient was having hemorrhages from the nose and mouth. She was given four transfusions, the last on January 21, after which she showed gradual improvement, with, however, a relapse about six weeks later, but this lasted only for about a week. The last examination showed 92 per cent hemoglobin, 4,350,000 red cells and 5,100 white cells. In other counts the white cells reached 7,200.

Influence on Infections—The connection between benzene poisoning and the course of infections has been investigated by means of experiments on animals. These experiments have been reviewed. There is much in the literature of clinical benzene poisoning to confirm the observations. Thus Rohner and his colleagues noted as an outstanding feature the decided lack of response on the part of their patient to infection. Hunter said that in his first two fatal cases the patients had septic temperatures, while two that recovered did not. Unfortunately blood cultures were not obtained, but he believed that possibly unrecognized sepsis caused the temperature, and that because of the extreme depression of the leukocytic defense the usual local manifestations of sepsis were wanting. This is in line with the observations made by Camp and Baumgartner on the course of infection in benzenized animals. Meda's patient had a prolonged suppurative cystopyelonephritis, which Meda believed to be directly connected with and influenced by the benzene. At a point in the disease when the red count was only 600,000 and the hemoglobin 15 per cent, with no youthful forms and no platelets the white cells numbered 3,000. Cystopyelonephritis then developed, with abundant suppuration, a typical temperature curve, and a rise in the white cell count to 7,300. Meda thought that the suppurative process was favored by the lowered resistance of the patient but that the benzene also acted as a stimulant to the blood-building tissues.

Smith's "case 4" was that of a woman who had a mass of suppurating lymph nodes in the axilla, which did not yield to treatment but persisted to the latest report more than five months after her discharge from the hospital. In Smith's "case 33" the patient had a white count of 2,200 with only 49 per cent polymorphonuclears. A few months

later an abscess of the left thigh developed, and the proportion of polymorphonuclears rose to 77 per cent, although the absolute count was increased only to 3,800

Many lesions of the mouth, some of them very severe, are described in these histories. These may be scorbutic ulcers or gangrenous patches and abscesses on the lips or in the pharynx. Vincent's angina was noted in several cases. The first patient of Anderson, Boyd and Jackson had a hematoma of the lip, which suppurated progressively till death. Ronchetti's first patient had an extensive scab over one tonsil surrounded by an area of inflammation and hemorrhage. In Oettinger's second case the most serious symptom was a large and destructive ulcer in the throat, which took two months to heal. In Martland's ninth case there was marked buccal sepsis, osteomyelitis of the lower jaw and gangrenous stomatitis. Vincent's organism was found.

At the International Congress of Occupational Diseases in Amsterdam in 1925, Floret reported a case of chronic benzene poisoning, fatal in which there were necrotic areas not only in the mucous lining of the mouth and throat, but also in the gastric mucosa. Loewy's case is unusually interesting. He said that benzene poisoning resembles scorbutus in respect to hemorrhages in the skin and mucous membranes, but that there is also a necrotic action. He reported a death from necrosis of the jaw resulting from benzene poisoning which he said was the first to be recorded in the literature (Martland's case, already cited, has not yet been published). The history was as follows:

The patient had repaired rubber with benzene cement for eighteen years, but was ill for three weeks, with pallor, anorexia, pain and swelling in the right upper jaw, fever and for three days dimness of sight in the right eye. The temperature ranged from 38.1 to 40.1 C (100.6 to 104.2 F). The pulse rate was 132, the respiration rate, 32. There were extensive redness, swelling, tenderness and fluctuation in the upper jaw extending over the lower, with crusts and scales in the mouth, and fetid breath. The spleen was not palpable. There was retinal hemorrhage. The blood count was as follows: red cells, 1,300,000; hemoglobin, 3.08 Gm; white cells, 1,800, with polymorphonuclears, 54 per cent, lymphocytes 38 per cent, large mononuclears and transitionals, 5 per cent, and eosinophils, 3 per cent. Death resulted from heart failure. At autopsy the diagnosis was gangrene of the lungs, gangrenous periostitis and osteomyelitis involving the antrum, acute splenitis, central fatty degeneration of the liver, ecchymoses in the endocardium and epicardium and anemia of the brain. The marrow of the femur was half yellow fat, half grayish red.

Loewy said that from the blood picture and the history of exposure this was clearly a case of chronic benzene poisoning. The action of benzene aided and accelerated the course of the infection partly through the resulting poverty of the blood and partly through the harmful effect on the biologic resistance of the mucous membrane of the mouth which must have been caused by benzene fumes.

McCord had under observation from 50 to 60 men using benzene "dope." None showed clinical benzene poisoning, but all showed evidence of a susceptibility greater than normal to ordinary infections, and McCord suggested that chronic benzene poisoning of low grade was responsible for this (personal communication to the author) ¹⁵

PATHOLOGIC ANATOMY

In the literature on chronic benzene poisoning, there are reports in greater or less detail of twenty-nine autopsies, and to these seven more may be added, one from the records of the Johns Hopkins Hospital (no 5425, January, 1918) sent to me by W G MacCallum, the other six from the records of H G Martland, Chief Medical Examiner of Essex County, N J. The cases in which the autopsies were recorded by Dr Martland occurred in the years from 1926 to 1928. He has allowed me to use his notes and comments.

The first autopsies reported were Santesson's, on two of his famous cases. In his first case, only petechiae in the epicardium and hemorrhage in the intestinal mucosa were significant. In his third case hemorrhages in the skin, pericardium, heart muscle and ovary were noted. Fluid blood was found between the intestinal coils and in the pelvis. The spleen was small and pale, the liver was soft and fatty. The marrow appeared normal in consistency and color.

The autopsy in the case of LeNoir and Claude comes next. They found many small hemorrhages in the myocardium and endocardium and a large infarct in the right auricle. There was more hemorrhage in the mucous membranes than in the skin, especially in the stomach, intestines, nose and mouth. Hemorrhage was also found in the pleura, the right lung, lymphatic glands and the floor of the third ventricle, two hemorrhages were found in the brain and one in the medulla—probably the immediate cause of death. The only mention of the blood is that in the

15 After the completion of this paper Hayhurst and Neiswander (see bibliography) published the history of a case of benzene poisoning, unusually severe but ending in recovery. This case was worked up with great thoroughness and was, moreover, followed for a period of three and a half years. The case occurred in a rubber worker, and the chief features were as follows: profound anemia, with the red cells numbering 900,000, leukopenia, with the white cells numbering 850, thrombopenia, with the platelets numbering 100,000, hemoglobin, 10 per cent, fragility decreased to 0.06 per cent from a normal 0.40 per cent, bleeding time more than twenty-five minutes, the result of a prothrombin test normal, coagulation time four minutes, no retraction of the clot after twelve hours, the result of a tourniquet test positive, blood cultures sterile. Transfusions of blood, a diet rich in iron and the administration of iron as medicament were followed by recovery. Three and a half years later, blood counts showed a normal picture except for moderate leukopenia (4,700 and 4,850 white cells), which was polymorphonuclear (mononuclears, 61 per cent and 60 per cent).

capillaries of the liver there was a marked abundance of leukocytes, chiefly mononuclears with deeply staining nuclei, apparently more numerous than the red cells, some of the latter were abnormal in color and shape

Autopsies were performed in both of Selling's famous cases. The first, made by W. G. MacCallum, showed bone marrow which "macroscopically did not look markedly hyperplastic." Microscopically few cells of any kind were seen. The red cells were chiefly normal, but pale, and there were very few leukocytes, mostly of lymphocytic and myeloblastic types, suggesting aplastic anemia. The second autopsy was made by M. Wintemitz. Here the marrow appeared hyperplastic, being of a deeper and darker red than that generally seen in hyperplasia, but the smears showed aplasia like that in case 1, though not of so marked a grade.

Zenoni reported on the pathologic changes in fatal benzene poisoning in three girls who had been employed in a raincoat factory. The features noted were hemorrhage in the skin, pericardium, endocardium and mucous membranes of the pharynx, esophagus and gastro-intestinal tract and in the urinary bladder, uterus, pleura, lungs, kidneys and bone marrow, general oligemia, parenchymatous and fatty degeneration of the myocardium, liver and kidneys, fatty marrow, fibrous though not enlarged spleen, and small and fibrous lymph glands. Histologically there was disappearance of myelocytes, myeloblasts with toxic leukolysis, partial disappearance of erythroblasts, fibrous spleen and lymph glands, with atrophy of follicles and thickening of trabeculae, and fatty degeneration of the capillaries. At the same meeting of the Lombard Medical Society at which Zenoni's paper was read, Genova also reported three fatal cases which at autopsy had shown aplastic marrow.

In Legge's two cases there were submucous hemorrhages in the intestinal tract and hemorrhage under the endothelium of the heart. In one changes characteristic of aplastic anemia were found on microscopic examination of the marrow of the long bones.

The case described by Laignel-Lavastine, Levy and Desoille was examined at autopsy. A marked dilatation of all the small blood vessels was found, especially marked in the visceral peritoneum. Many organs showed hemorrhage. The femoral marrow was yellow, fatty, the sternal, soft. The uterine lining was normal, but there was a clot of blood in the cavity, and in the left ovary there was a large hemorrhage like a blood cyst. Smears from the femoral marrow were poor in cellular elements, and most of the cells were lymphocytes, with a few leukoblasts and erythroblasts but no megakaryocytes. Smears from the sternal marrow were somewhat richer in cells of much the same character. The spleen showed great poverty of cells so that in spots the reticulum seemed empty. The sinuses were atrophic and empty, the

malpighian corpuscles reduced and the arteries sclerotic. The cells were lymphocytes with very few polymorphonuclears and no abnormal forms but there was an abundance of brown pigment perhaps precipitated there were also signs of "macrophagic pigmentaire," as also in the mesenteric ganglions. The liver had no excessive pigment and only slight cellular atrophy. A histologic examination of the cord stained by Nissl's method showed no abnormality.

Rohner's case showed two outstanding features at autopsy (1) a marked hemopoietic insufficiency and (2) a decided lack of response to infection. There was no evidence in the bone marrow of active formation of either red or white cells. The lymphoid system was less disturbed, the lymph nodes were small, with a paucity of lymphocytes. The Prussian blue reaction showed no definite increase of iron pigment in the liver, heart and kidneys, indicating that the action of benzene is greater on the blood-forming tissue than on the adult circulating elements. The purpuric hemorrhages were perhaps an evidence of a disturbance in the endothelial cells of the capillaries. The septicemia was a late event localized in the lungs and suprarenal glands. There was extensive bronchopneumonia, but microscopically the picture was not that of ordinary pneumonia, for no inflammatory cells were present although the alveoli were plugged with fibrin, which contained numerous organisms. The liver showed areas of focal necrosis in which there were organisms in abundance, but no inflammatory cells.

In Martland's second case autopsy showed aplastic marrow and lesions in the mouth. The same thing was true in his third case, and in addition small hemorrhages in the pericardium were shown. In his fourth and seventh cases there was extensive purpura, with hemorrhage in the pericardium and endocardium, and the marrow was aplastic. In the seventh case there were some bright red hemorrhagic spots in the marrow and hemorrhage in the pia mater. There were also buccal lesions in the seventh case.

Askey reported two cases of severe benzene poisoning in 1928, and later in a personal communication to me dated March 25 1930, he gave the concluding chapter in the history of case 2, and the report of the coroner's inquest on the case, which was as follows: "Petechial and various-sized hemorrhages in the skin, mucous membranes pericardium, and brain. The bone marrow was yellow and aplastic, the stomach and intestines contained blood."

Three unusual cases which came to autopsy, those of Loewy and Floret and Martland's ninth case are mentioned in the section on infection.

Typical aplasia of the marrow usually with some bright red points was found in nineteen cases. In that of Laignèl-Lavastine Levy and

Desoille the aplasia was not complete. In Loewy's case the femoral marrow was 'patchy,' half yellow and half grayish red. In Santesson's third case the femoral marrow was normal in consistency and color, in Crémieu's case the sternal marrow was normal in appearance to the naked eye. In three cases the marrow appeared macroscopically hyperplastic. These were Selling's case, the case from the Johns Hopkins Hospital and Martland's eleventh case, which is described in detail in a later section. In Cabot's case 13391 the femoral marrow was fatty and showed no regeneration, but the marrow of the ribs was normal to the naked eye and under the microscope showed numerous normoblasts and occasional megaloblasts, but no megakaryocytes. Rivet and Guédé found a predominance of eosinophil polymorphonuclears and myelocytes over the neutrophil cells of both kinds in smears from the costal marrow. There were lymphocytes, small and medium, there were no nucleated red cells.

The kidney was seldom mentioned as showing anything abnormal. Landé and Kalinowsky found hemorrhage into the kidney, and Martland in his seventh case found hemorrhage in the pelvis of the kidney and in the tissue around.

The spleen usually showed atrophy, with marked loss of cellular elements, the atrophy affecting especially the malpighian corpuscles. Pigmentation was usually said to be absent. Martland said that the lymphoid tissue had practically disappeared from the spleen in his second and third cases. The acute splenitis in Loewy's case and the necrosis of the liver in Rohner's were attributed to the sepsis.

The liver usually showed no marked abnormality. In Flandin and Roberti's case there was an unusual condition, namely, a large and tender liver and a yellow tint to the skin. Oettinger described a small liver in his first case, with jaundice, and Anderson found in his third case acute yellow atrophy of the liver. Fatty degeneration of greater or less degree was found by Crémieu, by Loewy and by Smith in her case 33 in which marked fatty degeneration affected also the pancreas and heart. Abnormal pigmentation was rare.

It is strange that one finds so little about the condition of the vascular system in experimental benzene poisoning and in autopsies on cases in man. Santesson explained the hemorrhages as being caused by fatty degeneration of the capillaries, but in the extensive literature on the subject of experimental poisoning there is little or no mention of the condition of the capillaries. Rohner, Baldridge and Hausman said that the hemorrhages are perhaps an evidence of a physiologic disturbance of the endothelial cells of the capillaries. Landé and Kalinowsky believed that an injury to the blood vessels was indicated in their first case by the fact that the extravascular clotting time was normal.

(four and one-half minutes), though the bleeding time was over fifteen minutes, thus showing, not thrombopenia, but a disturbance in the clotting mechanism of the vessels

That benzene causes anemia, not by hemolysis, but by injury to the bone marrow has been an accepted fact since Selling published his experiments, yet in some histories of chronic benzene poisoning there are indications of the destruction of red blood cells. The evidence of hemolysis is usually stated to consist in (1) irregularly shaped red blood cells, (2) jaundice or yellow serum, (3) chills and fever with septic fluctuations, (4) enlarged spleen in protracted cases, (5) blood coloring matter in the urine, and (6) deposit of pigment in the liver, spleen, bone marrow and kidneys.¹⁶ All of these have been described in chronic benzene poisoning, except the enlarged spleen. To take them in their order

1 A marked irregularity of the red blood corpuscles, with numerous small forms was seen in Hunter and Hanflig's second and sixth cases, Martland's first and fourth, Anderson, Boyd and Jackson's second and third, Chambovet's fourth, the cases of Faure-Beaulieu and Levy-Bruhl and Lande and Kalnowsky, and two cases histories of which have been reported to me

2 It is evident that the icterus index is almost never taken in cases of benzene poisoning, for I find it mentioned only by Hunter and Hanflig and by Martland. In Hunter and Hanflig's second case the index was 2 in the first attack and 8 in the second, and the sclerae were slightly icteric. Their sixth patient had had jaundice six weeks earlier, and when he came to the hospital there was yellow tinting of the sclerae and the icterus index was 2. In their first case the serum was yellow, in the fourth, deep jaundice developed some days before death. Martland is the only other who mentioned the icterus index, in his second case, it was 7.2. Oettinger's first patient had slight jaundice. Flandin and Roberti found a yellowish tinge to the skin and a liver somewhat enlarged and tender. In Anderson's third case there was jaundice, and death was "apparently due to acute yellow atrophy of the liver." In one of the cases histories of which were reported to me the patient's skin was lemon-yellow. Cabot's patient (case 13391) showed jaundice a few days before death.

3 A septic fever with chills, without evidence of infection, is noted in many cases as in those of Selling, Ronchetti, Rohner, Baldrige and Hausman, Anderson, Boyd and Jackson, Hunter and Hanflig, Cremieu and Flandin and Roberti. In all instances in which blood cultures were made they were negative, even in the case of Flandin and Roberti, in

¹⁶ See Drinker, C. K. *Oxford Medicine*. New York: Oxford University Press, 1918, vol. 2, pt. 2, p. 509.

which the temperature curve was typical of sepsis, and in Hunter and Hanflig's first case, in which chills and a rise of temperature to from 104 to 106 F was followed by a transient rise in the white cell count, and in Selling's first case, which presented a picture of severe toxemia Lande and Kalinowsky at autopsy found no sign of sepsis, and they attributed the high septic temperature to the absorption of products of cellular decomposition

4 An enlarged spleen is never found in benzene poisoning, but may also be absent in hemolysis of short duration

5 Urobilinuria, intense, was noted in Ronchetti's second case and in one of Oettinger's

6 Abundant deposit of pigment was found by Laignel-Levastine, Levy and Desoille in the spleen, and by Neumann in the spleen, liver and bone marrow In Cabot's case 13321, Mallory found a spleen typical of toxic, hemolytic anemia

These evidences of destruction of red blood cells may, of course, be explained by the breaking up and elimination of the red cells from hemorrhages in organs and tissues ¹⁷

DIFFERENTIATION FROM OTHER DISEASES OF THE BLOOD

Ronchetti summed up the features of benzene poisoning briefly and with proper allowance for variations The typical clinical picture is one of progressive anemia with malaise epistaxis, then rapid decline, petechiae, hemorrhage from the stomach, intestines uterus, mouth and retina fever more or less intense, sometimes chills, eventually disturbance of the nervous system and death from anoxemia and heart failure with pulmonary edema There is erythropenia, which may reach an extraordinarily low level with absence in the circulating blood of youthful forms of red cells, the index may be low or high, there is leukopenia which may reach an extraordinarily low level and is especially at the expense of the polymorphonuclears with an Ainet swing to the right and an absence of myelocytes, myeloblasts and lymphoblasts there are decrease of the platelets, sometimes impressive, and slow coagulation of the blood, with no retraction of the clot The diagnosis depends greatly on the history of occupation From acute leukemia it is distinguished not so much by a low count, since so much is written now of leukemia leukopenica, as by lack of immature white cells In comparison with pernicious anemia, benzene poisoning is not so protracted in its course and usually presents more striking hemorrhage and greater leukopenia

A strictly defined detailed symptom-complex with a definitely outlined postmortem picture, has been accepted as characterizing chronic

¹⁷ See Frank E Berl *Klin Wchnschr* 52 961 1915

benzene poisoning, and all deviations from these patterns have been rejected as either not caused by benzene or as representing mixed conditions, i. e., benzene poisoning superimposed on myelogenous leukemia or on pernicious anemia, or even on agranulocytic angina. Thus cases have been rejected or considered highly dubious because, for instance, instead of aplastic marrow, hyperplasia was found, new cells being formed but not delivered to the blood stream. And this in spite of proved exposure to benzene. Yet, knowledge of the changes in benzene poisoning in man is based on less than thirty reported autopsies, not by any means all of which were reported in detail, even if they were thoroughly performed. It is true that a much larger body of data, and much more accurate, is available in the field of experimental benzene poisoning, and it is really more on the results of these experiments than on human material that the accepted picture of the pathologic action of benzene is based. But experimental benzene poisoning is not identical with poisoning in human beings. It is a clearcut leukopenia, resulting from an attack on the leukocyte-forming organs, the anemia being a minor feature, often not in evidence at all. In man, the anemia may be the dominating feature, it often is. In animals hemorrhage is usually absent, in man it is usually the most conspicuous symptom.

A much wider latitude is allowed in the so-called idiopathic diseases of the blood. Thus in "primary aplastic anemia" also called idiopathic or cryptogenic aplastic anemia or aleukia hemorrhagica or aregenerative anemia or hypoplastic anemia, it is admitted that the pathology is not always the same in all cases. To quote from Ordway and Gorham, "The marrow may be hyperplastic from failure of the marrow to deliver products into the circulation. Areas of hyperplasia may be found if many of the long bones are examined carefully. The long bones may show more or less aplasia, while sternum and vertebrae may be active because the aplasia may be terminal." In the case of chronic benzene poisoning described by Laignel-Levestre, Levy and Desoille, the femoral marrow was yellow and fatty, and smears were poor in cellular elements, but the sternal marrow was rosier and smears were richer in cells. In Loewy's case the femoral marrow was half yellow, half grayish red. In Santesson's third case the femoral marrow was normal in consistency and color while microscopically the only change mentioned was hemorrhage, and in Clemieu's case the sternal marrow was normal in appearance to the naked eye. In very few records of autopsies on victims of benzene poisoning is any mention made of an examination of the marrow of any bones other than the femur.

The truth is that primary aplastic anemia differs from the so-called secondary form only in having no known cause. Ordway and Gorham

made some attempt to distinguish benzene poisoning from the idiopathic form of aplastic anemia, saying that in the former the symptoms do not start in less than three weeks or in more than four or five months from the time the exposure occurred. But this is untenable. It may be that no case has thus far been reported as developing after an exposure shorter than four weeks, but tomorrow this may be no longer true and there are many histories of exposure lasting several years before the onset of clinical symptoms. Between "primary" and "secondary" aplastic anemia the only distinction at present is that in the case of the latter there has been exposure to a known toxic agent, such as benzene, radium or roentgen rays.¹⁸

The diagnosis as between benzene poisoning and pernicious anemia is usually regarded as clear and presenting little difficulty, since in the former there is aplastic anemia with no signs of regenerative activity on the part of the bone marrow during life and after death aplastic marrow is found, while in pernicious anemia there is hyperplasia with signs of abnormal activity of the marrow. It is, however, admitted that aplasia may be the terminal phase of pernicious anemia. It must also be admitted that the blood picture in benzene poisoning is not always one typical of marrow aplasia, for nucleated red cells may be present and also a fairly great variation in the red blood cells as to size, shape and staining properties. Nor can the development of symptoms indicating lesions of the central nervous system be regarded as a deciding point in the diagnosis of pernicious anemia in view of the histories of such cases of indubitable benzene poisoning as that of Faure-Beaulieu and Levy-Bruhl,¹⁹ Oettinger's second case and Landé and Kalinowsky's second case. In this connection it is interesting to quote a personal communication to me by Martland with regard to one of the ten cases of chronic benzene poisoning the histories of which he sent me.

This case clinically is one of a leukopenic aregenerative anemia occurring in an artificial leather worker where benzene was used. Two of his relatives working in the same plant also died with similar symptoms. The enclosed records show that he had two admissions to Newark City Hospital. Autopsy discloses a profound leukopenic anemia in which the bone marrow is red on gross examination and on microscopic examination shows a panmyelosis with considerable erythroblastic regeneration similar to that seen in pernicious anemia. There are also areas of regeneration in the liver similar to what Piney has described in pernicious anemia.

I have never seen or heard of a similar marrow in chronic benzene poisoning, but I am quite sure that this man died of this disease.

¹⁸ See Minot, p. 606, also Mallory quoted by Cabot in his report of case 13391.

¹⁹ Faure-Beaulieu and Levy-Bruhl quoted Dejerine and Andre Thomas, who in discussing the lesions of the spinal cord in pernicious anemia said that the lesions and symptoms do not belong to one special form of anemia, but are alike for all kinds.

Martland also informed me that he has another unusual autopsy record. This deals with a case also diagnosed clinically as one of chronic benzene poisoning, but at autopsy

I found an unusual form of gastro-intestinal leukemia, with no leukemic blood picture. For this reason I was forced to testify in court that while I personally felt that the cause of this man's death was chronic benzene poisoning, I could not state it with any degree of certainty, as to my knowledge such a condition has never been described before in benzene poisoning. But from my knowledge of the radium cases I think such an interpretation is quite possible.

Cabot and Mallory's case 13321, in which exposure to benzene was admitted, called forth a decided difference of opinion (Cabot inclining to benzene as the cause) because of evidences of activity of the marrow during life, such as youthful forms of leukocytes and of red cells, and at autopsy a hyperplastic marrow showing rapid production of both red and white cells.²⁰ It was plain that there was no lack of formation of new cells, but a failure to deliver them to the circulation, and this was held by Mallory to preclude a diagnosis of benzene poisoning.²¹

It is only in benzene poisoning that one finds this insistence on a strictly delimited postmortem picture and symptom complex. More extensive studies of other diseases of the blood have invariably led to the discovery of atypical cases and consequently to a widening of the definition. For instance, agranulocytic angina, which has been known only since 1922, has already a far larger number of carefully studied cases in its literature than has chronic benzene poisoning (Harkins has collected reports of about 150 cases from the literature and has added 8 of his own), and during the eight years in which this new disease has been studied, it has become evident that it is not a single clinical entity which is adequately covered by the definition originally formulated by Schultz, but that many cases present variations from Schultz' description.

Schultz' agranulocytosis consisted in high fever with necrotic infections of the throat, rapid exhaustion, slight jaundice frequently and

²⁰ Minot speaks of instances in which at autopsy the marrow showed hyperplasia when the observations on the blood had been much like those of aplasia and perhaps identical with it.

²¹ The diagnosis of benzene poisoning is further obscured by the frequent presence of Vincent's infection as a complication probably a much more common occurrence even than the records show, for it is plain on reading many of the histories that no effort was made to determine the nature of the buccal lesions. A Plaut-Vincent infection with agranulocytic anemia, thrombocytopenia and hemorrhage of greater or less degree, as described by Arnold, differs from the picture of chronic benzene poisoning only by the lack of a history of exposure to benzene. The cases of Floret, Loewy, Martland, Oettinger, Meda and others show how the presence of an infection may render the clinical picture of benzene poisoning obscure and far from typical.

granular leukopenia without anemia or thrombopenia. The victims were generally elderly women. As other clinicians added their reports, the picture slowly altered. Hueper found that not only the granulocytic, but the lymphatic, system also was affected, although the red cell count remained normal and also the number of platelets. According to McCord, however, hemorrhage and purpura are present in the greater number of cases of agranulocytosis, although the bleeding time and coagulation of the clot are likely to be normal. Buck's case was one of typical aplastic anemia, with red cells numbering 850,000, hemoglobin 19 per cent and platelets 100,000. Harkins regarded four of his cases as agranulocytic angina, but the other four, as granulocytopenia. In one of these there were anemia and evidence of hemorrhagic diathesis. Stocke divided the cases into three different groups, one group answering Schultz' description, a second showing the presence of anemia and the third, a tendency to hemorrhage.

Kastlin collected from the literature reports of forty-three cases with autopsy and added two. A fairly wide variation in observations appears from this collection, and Kastlin believed that still more variations would come to light as experience widened. Thus, although the white cell count absolute and relative, was almost unvaryingly low, showing a profound granulopenia with lymphocytes numbering to from 60 to 100 per cent, the red cell and platelet counts were not so uniform. Of thirty-three red cell counts, eight were low, of twenty-seven platelet counts, seven were low. In the autopsies the marrow was red in twenty-seven instances, fatty in six. In some cases there were petechial hemorrhages in the viscera, in two cases large hemorrhages in the bone marrow and lungs and in one case, a retinal hemorrhage. A clinical hemorrhagic diathesis was present in somewhat less than one fifth, jaundice in about one half, of these cases.

Again, in regard to the effect of irradiation on the blood, which has been the subject of much study, it is now evident that the pathologic changes in experimental exposure to the x-rays or to radium are not the same as those observed in man, and that the latter differ in different persons (Evans and Roberts). Animals exposed to these rays suffered a marked destructive effect on the lymphatic system and the circulating lymphocytes (Warthin) and little if any, effect on the bone marrow, human subjects show a relative lymphocytosis, no demonstrable injury to the lymphatics, but a profound aplasia of the bone marrow, with granular leukopenia and aregenerative anemia (Carman and Miller, de Laet). Yet here, also the picture is not always typical, aplastic anemia is found in the greater number, but not always. Martland in his study of radium poisoning in painters of dials found two cases of it, but in five others the anemia was of the regenerative type with hyperplasia of the bone marrow.

Lymphatic leukemia was found by von Jagic and his colleagues and by Caiman and Miller, Weil (quoted by de Laet) had two cases of myeloid leukemia, Vaquez (quoted by de Laet), one of the same form while Brule and Boulin said that pernicious anemia has been described in some cases. Perhaps the most interesting report of all is that of Weil and Lacassagne (1925), for they told of two research chemists, who worked together, but not with exactly the same degree of exposure, first with radium, then with thorium X, and in both fatal disease of the blood developed, but in one it was typical myeloid leukemia in the other, aplastic anemia.

In most of these cases no thrombopenia or hemorrhage was observed, but in one of Martland's cases both were present, the Danish radiologist, Noindentoft, had thrombopenia (Faber) and so did Larkins' patient. It seems therefore clear that in injury from irradiation the attack may be directed now to one part of the blood-forming centers now to another or may involve all simultaneously.

Farley, in his study of agranulocytosis following arsphenamine therapy, suggested the term "depressed bone marrow function" for those cases that exhibit injury to one or another of the hemopoietic functions of the marrow or a combined attack on all. According to him, it is impossible to include under any less general head the many forms that have been described i. e., aplastic anemia, purpura hemorrhagica and agranulocytic angina with necrotic lesions in various parts of the body.

In this paper instances have already been given of benzene poisoning with atypical features, showing that the attack may be now on one, now on another, part of the blood-building system. To these may be added two more, the first of which is, so far unique, a case of leukemia attributed to benzene poisoning. Deloie and Borgomano, whose article I have been unable to read in the original, described according to Ballotta, a case of unusually slow benzene poisoning which resulted in typical leukemia instead of aplastic anemia. This occurred in a man who for many years was exposed continually to benzene in his work, but to small amounts. He died of acute leukemia. The authors believed that this paradoxical phenomenon—leukemia produced by an agent that is used in the treatment of leukemia—is to be explained by an inverse action of benzene when given in small doses as compared with what is seen when larger doses are given. There is also probably a wide variation in the response of individuals to the action of benzene.

The second case conformed in its earlier stages, to the typical picture of idiopathic purpura hemorrhagica, with the disease process directed to the platelets. This history came to me from the Johns Hopkins Hospital where the patient was treated in 1918.

A woman, aged 54, had worked for thirteen weeks in the scaling room of a can factory which later on was the source of several cases of severe benzene poisoning, from the benzene-rubber cement used as a scaling compound. This woman came to the hospital with a history of bleeding from the gums and nose for the preceding four days, dimness of vision and increasing weakness. There were purpuric spots over the limbs and double retinal hemorrhage, the bleeding time was twenty minutes, but the red cell count was 5,000,000, hemoglobin, 100 per cent, white cell count, 6,990, with 61 per cent polymorphonuclears, and the only abnormal feature in the blood picture was the almost total absence of platelets. Later, anemia and leukopenia developed, and the patient died at the end of a month, after eight transfusions. The marrow in this case was described as showing "myeloblastic aplasia and erythroblastic hyperplasia." The upper ends of both femurs were examined, the marrow was of extremely soft consistency "chocolate red in color." Microscopically, it was largely fat, the capillaries were filled with blood, there was evidence of hemorrhage, with little blood formation in the shape of small clumps of myelocytes and nucleated reds.

If it is true that wide variations are found in the pathology of diseases of the blood which have been the subject of extensive study, it seems that one is justified in believing that further study of chronic benzene poisoning will reveal a less one-sided picture than is at present accepted. The simple, unvarying picture of this form of poisoning as it is found in the textbooks is certainly based on insufficient human material. The greater part of the careful, detailed work on the action of benzene has been carried out on animals in the laboratory and for the most part with the employment of a technic which does not in any way reproduce what takes place in industrial poisoning of human beings. The victims of industrial poisoning whose bodies have come to autopsy are few in number, and their cases have not received as careful study, except in rare instances, as have the cases of such nonindustrial diseases as agranulocytic anemia and the so-called idiopathic anemias and leukemias, and lesions caused by irradiation.

APLASTIC ANEMIA FROM ARSENOBENZENES

It is not usual to include in a discussion of the pathology of benzene poisoning those rare cases of purpura hemorrhagica with aplastic anemia and leukopenia which have followed the administration of arsenobenzene, arsphenamine, etc. These accidents are by most authorities attributed to the action of arsenic. Labbe and Langlois, Moore and Keidel and Ordway and Graham all gave arsenic as the cause. Gorke also stressed the arsenic as the more important causative agent but admitted that benzene may play a part. Farley, on the other hand, believed it more probable that the action is due to a "benzene-like action," and Ronchetti held that benzene is the active agent.

To attribute to arsenic in any of its forms a destructive action on the blood-forming tissues with a resulting aplastic anemia is to controvert the beliefs of all the toxicologists. Arsenic has a marked destruc-

tive action on the blood only when it is in the form of arsine (As H_3), and then its action is hemolytic. Arsine belongs to the group of inorganic hemolysins, of which it is one of the most powerful (see Kobert, pp 246 and 735). The result is a secondary anemia, accompanied by a great increase of bile pigments in the serum and urine, enlargement of the liver and spleen and icterus of the skin and organs, followed by changes in the liver and kidneys, which are caused by the efforts of these organs to eliminate the debris of the red blood corpuscles.

This is a condition altogether different from that described by those who have studied the aplastic anemia following injections of arsphenamine, etc. What they describe is a condition indistinguishable clinically from the aplastic anemia of chronic benzene poisoning. Farley called it "depressed bone marrow function from the arsphenamines." There are anemia, which may be profound (with the red counts as low as 600,000, as in the case of Emile-Weil and Isch-Wall), leukopenia (with a white cell count as low as 600, as in Gorke's case) which is agranulocytic (the polymorphonuclears falling as low as 4 per cent, as in Moore and Keidel's case), a marked loss of platelets and, clinically, purpura hemorrhagica. Emile-Weil and Isch-Wall's patient had hemorrhages from the uterus and the lungs and purpuric spots on the skin. Gorke's first patient had bleeding from the gums and uterus and suffusion of blood under the skin. His second had bleeding from the mouth and nose. In Frank's case (see Gorke) there were multiple hemorrhages under the skin and blood in the stools. Gorke called the condition hematomyelopathy with extreme neutropenia and thrombopenia and a hemorrhagic diathesis, analogous to the anemia of benzene poisoning and anemia radiotoxica.

Scorbutoid ulcers in the mouth, with a diphtheroid membrane, were described by Gorke, ulceration of the tonsils, with a pseudomembrane, by Emile-Weil and Isch-Wall, necrotic ulcers of the mouth, lips and nares, by Moore and Keidel—all of which, according to Farley, show the result of destruction of the patient's active immunity.

Farley discussed seven cases in which the clinical picture varied according to the degree of "marrow depression" and according to the particular element or elements of the marrow most affected. Since the first case was described by Labbe and Langlois, thirty-nine have been reported. They show many forms of depressed function of the bone marrow following the administration of arsphenamine, such as aplastic anemia, purpura hemorrhagica and agranulocytic angina. These cases are rare, they probably occur in persons with a congenitally weak hemopoietic apparatus, and secondary infection plays a large part in the more serious cases. The aplasia may be really only a temporary depression of the marrow as is shown by the successful use of transfusions of blood.

Failey held that the cause is a disintegration in vivo of the arsphenamines, so that a benzene-like action takes place. This is a matter of opinion, not of proof, but it seems unlikely that arsenic should be responsible. The cases belong to the group of symptomatic dyscrasias of the blood resulting from the action of benzene, radium and roentgen rays but resemble most strongly the first-named.

No explanation of these cases can as yet be given. Carl Voegtlin, consulted on this point, wrote as follows:

We have good reason to believe that any toxic effect, no matter on what organ, produced by these arsenicals is essentially due to the arsenic in firm combination with the benzene nucleus. On chemical and pharmacological grounds I cannot conceive the possibility of benzene, as such, being formed in the animal body after the introduction of any of the arsphenamines.

We have shown that the only directly acting modifications of these arsenicals are the trivalent arsenious oxides ($C_6H_5OHAsO_2NH_2$). We still lack information as to the possible changes occurring in the ortho-amino phenol grouping of these drugs.

So far it has been impossible to produce experimentally in animals a condition resembling aplastic anemia observed in syphilitics. Why, on rare occasions, a patient develops aplastic anemia as a result of arsenic treatment I am unable to say. It would seem, however, that this occurs only in cases that show peculiar and not understood constitutional idiosyncrasies.

Moore and Foley discussed the resemblance between these accidents occurring in the course of arsenobenzene treatment and benzene poisoning.

There is a certain superficial analogy between the blood pictures and the microscopic picture of the bone marrow that we have reported with those of benzole poisoning.

Salvarsan of course contains a double benzol ring but no evidence can be found to show that in the body it breaks down into benzol. Investigation of its known products of decomposition along the lines of their selective toxicity for the bone marrow would be well worth while.

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Notes and News

University News, Appointments, Promotions, Resignations, Deaths, etc—Konrad E. Birkhaug of the department of bacteriology in the University of Rochester school of medicine and dentistry has been elected a member of the Norwegian Academy of Sciences.

Frederick Eberson has been made director of the clinical laboratories at Mount Zion Hospital, San Francisco, and Glenville Y. Rusk has been placed in charge of the department of pathology.

Rigney D'Aunoy has been appointed professor of pathology and bacteriology in the newly organized medical school of the Louisiana State University.

Kenneth B. Hanson has resigned as instructor in pathology and bacteriology in the school of medicine of West Virginia University at Morgantown.

Emery R. Hayhurst has resigned as professor of public health and hygiene in the Ohio State University.

The Paul Ehrlich-Stiftung has awarded the Paul Ehrlich gold medal to C. Levaditi of the Pasteur Institute in Paris for his work on chemotherapy.

Sir Charles Martin has retired from the directorship of the Lister Institute for Preventive Medicine. He is now in Australia to inaugurate and direct, for a period of two years, a governmental organization for research into animal nutrition.

D. F. Cappell, now lecturer on pathologic histology in the University of Glasgow, has been appointed professor of pathology in the University of St. Andrews.

E. G. D. Murray of the department of bacteriology in Cambridge University has been made professor of bacteriology in McGill University, Montreal.

M. W. Beijerinck, the Dutch bacteriologist who discovered that the so-called mosaic disease of the tobacco plant is caused by an ultramicroscopic, filtrable virus, has died at the age of 79.

Chung Yik Wang, professor of pathology in the University of Hong-Kong since 1920, has died at the age of 42. He was educated at Queen's College, Hong-Kong, and in medicine and public health at Edinburgh and Manchester Universities.

Sir Andrew Balfour, director of the London School of Tropical Medicine, formerly director of the Wellcome Tropical Research Laboratories at Khartoum, distinguished investigator and administrator in the field of tropical medicine and hygiene, has died at the age of 58.

Archibald Leitch, director of the department of research in the Cancer Hospital, London, and successful investigator of experimental carcinogenesis, has died at the age of 52.

Scientific Societies—The Second International Congress of Comparative Pathology will meet in Paris, Oct. 14 to 18, 1931. The secretary of the American committee is George W. McCoy, National Institute of Health, Washington, D. C.

At the recent meeting in Boston, the Society of American Bacteriologists elected officers as follows: J. Howard Brown, president, L. A. Rogers and Norman MacL. Harris, members of the council.

On July 1, 1930, there were 399 members in Die Deutsche Pathologische Gesellschaft. At the last meeting of the society, the governing body adopted a recommendation setting the occasion for homage volumes (Festschriften) at the seventieth birthday of the dedicatee and limiting the authorship to pupils of the dedicatee.

An International Leprosy Association has been organized with Victor G. Heiser as president, and a journal on leprosy is to appear with H. Windsor Wade as editor.

The Pasteur Society of Central California has elected the following officers: president, W. H. Manwaring, vice-president, W. T. Cummins, and secretary-treasurer, Beatrice Howitt.

At the twenty-sixth annual meeting of the German Pathological Society in Munich, April 9 to 11, 1931, the importance of tissue culture in pathology was discussed by G. Herzog and A. Fischer.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

CALCIUM CHANGES IN THE BRAIN IN ETHER ANESTHESIA EDMUND ANDREWS,
WILLIAM F PETERSEN and REUBEN I KLEIN, Ann Surg **92** 993, 1930

Ether anesthesia in dogs is accompanied by a marked rise in the calcium in the brain as well as in the liver. These changes are probably to be interpreted as meaning a lesser activity and irritability of the brain cells due to changes in the mineral salt content in the cells themselves

AUTHORS' SUMMARY

THE INFLUENCE OF URIC ACID ON THE PERMEABILITY OF MEMBRANES V
CHINI, J Exper Med **53** 1, 1931

Congo red injected in vivo together with uric acid gives rise to more intense and diffuse red coloring in rats, especially in the subcutaneous and peri-articular tissues, than is the case in control rats given injections simply with dye. Uric acid added in vitro to solutions of congo red or trypan blue increases the speed of diffusion of these dyes, both through gelatin and the animal membranes (dialyzers). These results support a view long maintained by Rondoni, namely, that some factor of an endothelial-capillary nature must be taken into consideration in manifestations of hyperuricemia and of gout

AUTHOR'S SUMMARY

A CEREBELLAR DISORDER IN CHICKS, APPARENTLY OF NUTRITIONAL ORIGIN
A M PAPPENHEIMER and M GOETISCH, J Exper Med **53** 11, 1931

Growing chicks maintained on a diet consisting of milk powder, casein, starch, yeast, cod liver oil, salts and filter paper develop ataxia, tremors, retraction or twisting of the head, clonic spasms of the legs and stupor. These symptoms may appear suddenly, usually between the eighteenth and twenty-fifth day, and may end in death. If recovery takes place, the chicks may go on to normal development. Definite lesions are found in the cerebellum of the affected chicks. These consist of edema, necrosis and hemorrhages. Hyaline thrombi are found in the capillaries in and about the degenerated areas

AUTHORS' SUMMARY

SEASONAL VARIATIONS IN THE GOITER OF RABBITS PRODUCED BY FEEDING
CABBAGE B WEBSTER, D MARINE and A CIPRA, J Exper Med **53** 81,
1931

The evidence presented indicates that cabbage maturing in the spring and summer months has little goiter-producing power. Cabbage maturing in the late autumn has much greater goiter-producing power, although this shows considerable variation in different years. It has not been possible to correlate available meteorologic data with these variations

AUTHORS' SUMMARY

ABSORPTION FROM THE PERICARDIAL CAVITY C K DRINKER and M E
FIELD, J Exper Med **53** 143, 1931

Physiologic solution of sodium chloride is absorbed from the pericardial cavity of medium-sized rabbits at a rate of approximately 13 cc per hour. This absorption is via the subepicardial blood capillaries. Rabbit serum and horse serum are absorbed extremely slowly—an indication of the low grade lymphatic drainage of the pericardial sac. Graphite particles of bacterial dimensions are also removed

slowly. Such particles enter the lymphatics only after phagocytosis. The lymphatics in the basal part of the pericardium are the principal source of drainage. Subepicardial lymphatics are entered with difficulty from the pericardial cavity.

AUTHORS' SUMMARY

FIXATION BY THE INFLAMMATORY REACTION V MENKIN, J *Exper Med* 53 171 and 179, 1931

Microscopic studies show the presence of a network of fibrin within the tissues and numerous thrombosed lymphatics at the site of inflammation. Precipitated iron compounds, possibly coagulated horse serum, or particulate matter caught in this fibrinous reticulum will disseminate less readily than trypan blue from the site of inflammation. Trypan blue injected at the periphery of an inflamed area fails to enter the site of inflammation. This failure to penetrate is caused by the occlusion of lymphatic vessels and by the presence of a fine network of fibrin in the tissue spaces of the inflamed area. Fixation of foreign substances by the inflammatory reaction is, therefore, primarily due to mechanical obstruction caused by a network of fibrin and by thrombosed lymphatics at the site of inflammation. There is another phase of the problem which still requires more accurate information. This concerns the relation between exudation from blood vessels and changes in flow of lymph from the inflamed area. Further experiments are being conducted to investigate this question. The reaction of fixation, which occurs extremely early in the inflammatory process, circumscribes the irritating substance and allows a definite period of time for the leukocytes to assemble for the purpose of phagocytosis. It is through a delicate regulating mechanism of this kind that, to use the expression of Opie, "the vital organs are protected at the expense of local injury."

Trypan blue injected into the circulating blood stream of frogs accumulates rapidly in an inflamed area. When trypan blue is injected directly into the area of inflammation, it is fixed *in situ* and fails to diffuse outward. If the dye is injected at the periphery of an inflamed area, it fails to enter the site of inflammation. This failure of penetration is caused by the occlusion of lymphatic vessels and the presence of a network of fibrin in the inflamed area. These experiments furnish additional evidence that fixation of foreign substances by the inflammatory reaction is due to mechanical obstruction caused by a network of fibrin and by thrombosed lymphatics at the site of inflammation.

AUTHOR'S SUMMARY

THE GRADIENT OF VASCULAR PERMEABILITY P ROUS and F SMITH, J *Exper Med* 53 195 and 219, 1931

A mounting gradient of permeability exists along the capillaries of the muscles of the frog. In the muscles of the chicken none has been demonstrated, but the close-knit vascularization is arranged in duplicate in such manner that the blood runs in opposite directions through the capillaries of nearly adjacent fibers. In a flight muscle of the pigeon there exists, in addition to this artifice, what appears to be a special collecting system of venous capillaries. In the mammalian diaphragm indications of such a system are also to be found, and a gradient of capillary permeability like that in the other skeletal muscles is probably present. These vascular conditions are briefly considered in terms of function.

A steeply mounting gradient of permeability is demonstrable along the meshwork of capillaries that connects the arterioles and venules of the skin of the frog. The venules incorporated in the meshwork are even more permeable than the capillary meshes giving into them. The presence of the gradient under such differing conditions as exist along the capillaries of frogs and mammals enables one to rule out certain factors that might be invoked to explain it, and it is not explainable in terms of those influences generally recognized as conditioning exchange between the blood and tissues. Not improbably it results from a structural differentiation along the capillary.

AUTHORS' SUMMARY

GRAVES' CONSTITUTION (WARTHIN) C A HELLWIG, Surg Gynec Obst **52** 43, 1931

Study of thyroid glands, obtained at autopsy and by surgical removal, did not support the contention of Warthin that status thymicolymphaticus is associated with lymph follicles in the thyroid gland. In only 66 per cent of cases of exophthalmic goiter and toxic goiter was there lymphoid tissue in the thyroid gland, and of the cases without clinical symptoms of thyrotoxicosis 38.5 per cent showed lymphocytic infiltration. Two cases of sudden death with all the anatomic signs of a thymicolymphatic constitution failed to show any lymphoid tissue in the thyroid glands. Lymphocytic infiltration of the thyroid is not a manifestation of an underlying constitutional anomaly but a local response to hyperplasia and hypersecretion of the gland as indicated by the facts that lymphocytes collect only in or around the islands of cellular hyperplasia and that the colloid-rich areas are practically free from round cells.

RICHARD A. LIVENDAHN

CARBOHYDRATE METABOLISM IN TUBERCULOSIS I. E. RABUCHIN, Beitr z Klin u Tuberk **74** 541, 1930

Both in experimental and in extensive pulmonary tuberculosis the carbohydrate metabolism is decreased. The impairment is due to a dysfunction of the liver and of the suprarenal system. In experimental tuberculosis in guinea-pigs there is hypofunction of the pancreas. The condition of the carbohydrate metabolism justifies the therapeutic administration of insulin.

MAN PINDER

STUDIES ON THE PHYSIOLOGY OF SEX M. BORST, A. DODERLEIN and D. GOSTIMIROVIC, Munchen med Wchnschr **77** 473, 1930

In order to determine whether the anterior hypophyseal hormone can produce changes in the immature male mouse, such as have been described for the female, the authors tried to answer the questions whether manifest changes could be produced within an average of 100 hours and what portion of the testicular apparatus was first stimulated or changed. In this communication the results of various dosages of the hormone on immature mice are given. Contrary to the observations of both Herman and Saller, the authors were able to observe spermatozoa as early as the twenty-seventh day of life. Weak doses (from 3 to 6 rat units daily) had no effects, but dosages ranging from 30 to 200 rat units daily produced definite effects. Within 100 hours the following changes could be made out in the testicle and seminal vesicle: (1) increased mitotic division of spermatogonia, as well as of spermatocytes, with areas of detachment and fusion of cells, and (2) increased size of the glandular lining of the seminal vesicle, with much mitosis in its epithelium, as well as a striking increase in secretion.

A. J. KOBAC

THE PERMEABILITY OF THE BLOOD VESSELS OF THE EYE AND BRAIN FOR ACID AND BASIC DYES P. N. WESSELEIN, Ztschr f d ges exper Med **72** 90, 1930

Experiments revealed that the blood vessels of the eye were readily permeable for basic dyes, while acid substances passed through with difficulty.

PEARL ZEEK

BASAL METABOLISM IN UNDERFEEDING M. RUBNER, Ztschr f d ges exper Med **72** 123, 1930

In the author's experiments underfeeding did not lower the basal metabolism. There were noteworthy changes, however, in the nitrogenous waste and in the acid and ash content of the urine.

PEARL ZEEK

EFFECT OF TEMPORARY OCCLUSION ON BLOOD-FORMING TISSUE OTTO KAISER, *Ztschr f d ges exper Med* **72** 211, 1930

The arterial supply to large portions of bone marrow was occluded for varying lengths of time, and the effects on the various blood cells were studied. The contrast in the behavior of cells of the lymphatic and myelocytic series would indicate a dual origin of these two types of cells

PEARL ZEEK

THE ACTIVE SUBSTANCE OF DERMOGRAPHIA MAX HOLZAPFEL, *Ztschr f d ges exper Med* **72** 269, 1930

Following mechanical irritation of the skin a substance is formed which passes into the circulation, the action of which closely resembles that of histamine when the latter is injected subcutaneously into human beings

PEARL ZEEK

Pathologic Anatomy

THE PATHOGENESIS OF BROWN INDURATION OF THE LUNG ELI MOSHCOWITZ, *Am Heart J* **6** 171, 1930

Brown induration of the lung only occurs in the forms of circulatory or cardiac disturbance in which a hypertension of the pulmonary circulation can be predicated, no matter where the increased peripheral resistance may be. The lesions are exclusively associated with arteriosclerosis of the pulmonary vessels. Arteriosclerosis of the pulmonary vessels is, therefore, pathognomonic of hypertension of the pulmonary circuit and vice versa. The lesion of brown induration of the lung consists essentially in dilatation and thickening of the pulmonary capillaries. It is an "arteriosclerosis" in miniature. Unquestionably, part of the sclerotic process is the result of diminution in blood supply and even infarction of the affected areas. The lesions within the lung parallel exactly those seen in the systemic organs, and especially in the kidney, in hypertension of the greater circulation. A case is reported in which the lesions of the brown induration of the lung were found consequent to a prolonged asthma. Under observation, the patient revealed the transition from a purely functional bronchial asthma to emphysema, to a pure clinical example of hypertension of the pulmonary circulation and finally to death from failure of the right side of the heart.

AUTHOR'S SUMMARY

PATENT OMPHALOMESENTERIC DUCT ASSOCIATED WITH INCOMPLETELY PATENT URACHUS MILTON M AUSLANDER and LAURA McCLURE, *Am J Dis Child* **40** 1276, 1930

A case of patent omphalomesenteric duct is reported. The case was associated with the following unusual features: (a) occurrence in a premature female infant, (b) occurrence with an associated incompletely patent urachus, and (c) difficulty in feeding. Differential diagnosis between umbilical granuloma, patent urachus and patent omphalomesenteric duct is extremely important, especially from the point of view of treatment.

AUTHOR'S SUMMARY

A CASE OF ENCEPHALITIS AND INFILTRAL PNEUMONIA FOLLOWING VACCINATION RUTH TUTHILL, *Arch Neurol & Psychiat* **24** 759, 1930

The patient, a boy, aged 6, twelve days after vaccination against smallpox and after a headache of two days' duration became stuporous and incontinent and convulsions developed. On the fourth day of the illness, examination showed lateral nystagmus, spasmodic twitchings of the eyelids, cyanosis, tonic contraction of the extremities and physical signs of pneumonia. The blood contained 31,000 leukocytes per cubic millimeter. The temperature was 102 F, the spinal fluid was

under increased pressure and contained 12 cells per cubic millimeter. Death occurred on the fifth day after the onset of the disease.

Macroscopic and microscopic examinations revealed an influenzal bronchopneumonia in which Pfeiffer's bacilli were demonstrated, and marked perivascular infiltrations with lymphocytes, plasma cells and macrophages in the centrum semiovale and the lower layer of the cortex, with the extension of the infiltration cells into the parenchyma. The precapillaries were the vessels principally infiltrated. In the corpus striatum, globus pallidus, optic thalamus and pons very few vessels showed infiltrations. The substantia nigra was practically normal. In the cerebellum only the dentate nucleus showed perivascular infiltrations. The medulla and upper part of the spinal cord were normal. The infiltrated areas appeared demyelinated, and fat globules were practically absent throughout, only a few uninvolved vessels beneath the cortex showed them. The author explains the apparent demyelination around the blood vessels not by degeneration of the myelin fibers but by their being "pushed aside." She admits that the pathologic picture is not typical of postvaccinal encephalitis.

G. B. HASSIN

ENCEPHALOMYELITIS COMPLICATING MEASLES. H. M. ZIMMERMAN and HERMAN YANNET, *Arch Neurol & Psychiat* **24** 1000, 1930.

In a boy, aged 4, a picture of meningo-encephalitis developed on the fifth day of measles and was followed by death six days later. The microscopic changes in the brain were essentially like those described in so-called postvaccinal encephalitis—areas of demyelination without axonal changes, throughout the white substance of the brain, associated with marked proliferation of microglia and the transformation of the latter into granule cells and "polyblasts." The gray matter was hardly involved, hemorrhages and perivascular hematogenous infiltrations were entirely absent. The leptomeninges exhibited a mild mononuclear cell reaction, composed of transformed microglia cells that the authors think probably wandered in from the perivascular spaces of the cerebral parenchyma or the cranial nerves. The cortical gray matter, basal ganglia, red nucleus and substantia nigra were not affected.

G. B. HASSIN

INCLUSION BODIES IN ARTIFICIALLY INDUCED CONJUNCTIVITIS. S. R. GIFFORD and N. K. LAZAR, *Arch Ophth* **4** 468, 1930.

The authors succeeded in producing inclusion bodies in the conjunctivae of guinea-pigs and rabbits by creating an inflammation by means of *Bacillus pseudotuberculosis-odentum* as well as by chemical irritants such as 25 per cent nicotine or pure croton oil. These inclusions are, in the opinion of the authors, identical with those observed in trachoma and "inclusion blennorrhea." "The presence or absence of inclusion bodies would hence appear to be of no importance in the etiology or diagnosis of trachoma."

CHARLES WEISS

ON THE ORIGIN OF MILIARY ANEURYSMS OF THE SUPERFICIAL CEREBRAL ARTERIES. WILEY D. FORBES, *Bull Johns Hopkins Hosp* **47** 239, 1930.

Miliary aneurysms of the superficial cerebral arteries and most probably those of all other arteries of medium size occur independent of an inflammatory process, arteriosclerosis or external trauma, and these aneurysms as such are not congenital malformations. That they are acquired lesions arising from a combination of focal weakness in the wall of the vessel, resulting from a congenital defect of the muscularis and degeneration of the internal elastic membrane, due to continued overstretching of this membrane, seems the most logical conclusion. While this point of view is maintained, the fact remains that there are aneurysms of the small blood vessels due to arteriosclerosis, trauma, syphilis, bacterial infection, etc. These aneurysms, however, are sufficiently characteristic to allow easy recognition,

and hence they need never be confused with those of the specific group, which themselves are characteristic in their location, multiplicity, size, microscopic structure and other features

FROM AUTHOR'S SUMMARY

SPONTANEOUS CARDIAC RUPTURE E H BERGFORD and C J C EARL, *Quart J Med* **23** 55, 1930

"The literature on the subject consists mainly of a large number of reports of isolated cases or very small series, published frequently by quite unskilled observers struck by the dramatic aspect of the condition" The first thirty-two cases of this series of forty-six cases among inmates of a hospital for the insane were not studied carefully histologically, the last fourteen cases were carefully studied Of the latter, every one showed recent infarction In only two cases was there any evidence of beginning repair Thrombosis of the coronary supplying the infarcted area was definitely demonstrated in nine instances Autopsies of the thirty-two earlier cases made no mention of infarction, showing the necessity for careful microscopic examination The percentage of women (82.2 per cent) was higher in this series than in previous reports

The authors call attention to the fact that antemortem history is usually one of coronary occlusion and not rupture, also that rupture is one of the less frequent sequelae of cardiac infarction (about 6 per cent) They believe that hemorrhage into the softened infarcted area, and into areas of fat necrosis, plays an important role in the mechanism of the rupture Raised intrapericardial pressure cannot be the cause of death in all instances, the amount of blood in the pericardium being small in many cases

ROY F FLEMSTER

HISTOLOGIC STUDY OF NEARTHROSIS FOLLOWING FRACTURE OF THE NECK OF THE FEMUR E FREUND, *Beitr z path Anat u z allg Path* **85** 101, 1930

Freund describes in detail the changes that occur in the opposed surfaces of the two fragments in fracture of the neck of the femur and that lead to the formation of a nearthrosis His study is based on material from nine cases in which the age ranged from 56 to 79 years, five were cases of tabetic arthropathy Even when the round ligament is torn across and the head loses all connection with surrounding tissues and acts as a foreign body, reparative changes occur in the fracture surface When the head retains connections that afford a better nutritional supply, the reparative phenomena in the fracture surfaces of the head and shaft lead to the formation of articular surfaces, in which process connective tissue, cartilage and bone take part in varying degree A joint capsule is formed that may also contain areas of cartilage or bone A synovial membrane is formed Where this is subjected to mechanical pressure or stress, adipose tissue is laid down, a fact that suggests that the fatty pads of the synovia of normal joints have a protective function

O T SCHULTZ

CHANGES IN THE BONE MARROW IN AGRANULOCYTOSIS E OPPIKOFER, *Beitr z path Anat u z allg Path* **85** 165, 1930

In three cases of fatal agranulocytosis studied histologically Oppikofer noted that the disappearance of the leukocytes is uniform in all the tissues and organs of the body The disappearance of the leukocytes is due to the action of some as yet unknown toxin on the myeloblasts of the bone marrow These cells reveal various forms and degrees of degeneration leading to necrobiosis Degeneration and destruction of the myeloblasts are the characteristic and essential changes in agranulocytosis The spleen in Oppikofer's cases revealed a plasmatic reaction, without a local formation of granulocytes

O T SCHULTZ

HYPOPHYSAL DWARFISM IN A FEMALE F ALTMANN, Beitr z path Anat u z allg Path 85 205, 1930

Chief interest attaches to the case reported by Altmann because he claims it is the first well authenticated example of pituitary dwarfism in the female in which changes in the internal genitalia received full consideration. The girl was 17 years old at the time of death. Growth had been normal until the eighth year of life, when she began to have headaches and to complain of difficulty with vision. These symptoms increased slowly but progressively and led to admission to the hospital, where death occurred within a few days. The patient was 129 cm tall, a height which corresponds to that of a normal girl of 10 years. The breasts were undeveloped, and the axillary and pubic hair was absent. She had never menstruated. The basal metabolic rate was normal. There was bilateral optic atrophy. Roentgenographic examination revealed a normal sella, above which was an area of calcification. The clinical diagnosis of tumor of the hypophyseal duct was confirmed at necropsy. The tumor was the size of a hen's egg, was largely calcified, contained squamous epithelium, and had caused compression atrophy of the anterior lobe of the pituitary. The tumor exhibited evidence of progressive expansive growth, but was not considered malignant. The thymus was incompletely involuted. The thyroid, parathyroids and suprarenals were normal. The ovaries weighed 34 and 32 Gm, respectively, and each contained many small cystic follicles. Developing follicles were numerous in the ovaries, but maturation and rupture of follicles had not occurred and there were no recent or old corpora lutea. The uterus was infantile. Altmann's interpretation of these observations is that the tumor caused atrophy of the anterior lobe of the pituitary and deficiency of anterior lobe hormone. Development of ovarian follicles was normal to the stage of maturation and rupture of follicles, which processes require the action of pituitary hormone. The incomplete development of ovarian follicles led to deficiency of ovarian hormone, which in turn resulted in failure of development of the uterus and mammae, in absence of axillary and pubic hairs, and in the nonestablishment of menstruation.

O T SCHULTZ

THE PATHOGENESIS OF ARTERIOSCLEROTIC CHRONIC INTERSTITIAL NEPHRITIS
M STAEMMLER, Beitr z path Anat u z allg Path 85 241, 1930

In the generally accepted view of the pathogenesis of that form of chronic interstitial nephritis that is due to arteriosclerosis of the larger branches of the renal artery, fibrosis of the glomeruli is the immediate result of the impaired nutrition due to narrowing of the arteries. Atrophy of the tubules is secondary and is held to be due to loss of function, and perhaps also in part to continuing poor nutrition of the tissue. In the incomplete infarction that follows partial thrombosis of an artery and in the peripheral zone of complete infarcts, according to Staemmler, the process is reversed. The tubules degenerate and undergo atrophy first. Fibrosis of the glomeruli follows the tubular changes. Since in complete and incomplete infarction the fundamental process is also one of lowered nutrition, Staemmler believed that it should be possible to find in kidneys with arteriosclerotic chronic interstitial nephritis, histologic evidence to determine whether the glomerular or tubular changes are first to appear. From the series of kidneys studied he selects three in which the changes were early enough to permit him to arrive at a conclusion as to the sequence of events. In these it was possible to find areas of tubular degeneration and atrophy, the glomeruli being intact. He concludes that the impaired nutrition that results from narrowing of the arteries leads first to tubular damage, and only later and secondarily to glomerular changes.

O T SCHULTZ

PARADOXICAL EMBOLISM AFTER LABOR W KOESSIN, Deutsche med Wchnschr
56 2081, 1930

A 30 year old primipara complained of sudden severe pain in the left leg eleven days after delivery, and shortly afterward the leg became cold and paralyzed. Symptoms and physical signs of an infarct in the right lung were noted about the same time. Because the left popliteal artery was pulseless, the left femoral and external and common iliac arteries were opened in an effort to remove obstructing thrombi. Postmortem examination disclosed thrombosis of the left femoral vein, an obturating thrombus of the right pulmonary artery, a patent foramen ovale, recent infarcts of the left kidney and a saddle thrombus (paradoxical embolus) at the bifurcation of the aorta obstructing both common iliac arteries.

PAUL BRESLICH

THE FATE OF INTRAVITALLY STORED DYESTUFFS KURT SOMMERFELD, Ztschr
f d ges exper Med 74 105, 1930

Experiments show that india ink injected intravenously may be recovered in apparently undiminished quantity from the body of experimental animals after 500 days. The stored dye, however, undergoes certain changes in position in the course of time, being sometimes found in the liver, while at other times it is absent in the liver and may be found in the spleen and bone marrow.

PEARL ZEEK

HEMANGIOMA AND HEMANGIOMATOSIS FRANCIS HARBITZ, Norsk mag f
lægevidensk 91 1335, 1930

Two cases of hemangioma of the eye (von Hippel's disease) are described, one in a 17 year old girl and the other in a man 55 years old. A hemangioma of the cerebellum in a boy, 16 years old, who died suddenly from hemorrhage into the fourth ventricle, is described, also a large cavernous hemangioma in the lower part of the spinal cord and the cauda with extensive hemorrhage in a woman 41 years of age. In no one of these last two cases were there any growths or cysts in the pancreas, the kidneys or the suprarenals. Two cases of multiple hemangioma of the liver in a man 36 years old and a woman 24 years old are described, in both of these patients the liver increased rapidly in size with abdominal pain, ascites and hemorrhagic diathesis, after death the liver in both cases was greatly enlarged and completely transformed into hemangiomata, in one of the cases there was metastasis in the lungs (hemangiosarcoma).

Pathologic Chemistry and Physics

BILE SALT HEMOLYSIS IN NEW-BORN INFANTS AND ITS INHIBITION BY THE
BLOOD SERUM HEYWORTH N SANFORD, MARIAN M CRANE and ELEANOR
I LESLIE Am J Dis Child 40 1039, 1930

The amount of bile salts necessary to cause hemolysis of the red blood cells of the normal new-born infant is fairly constant and practically the same as in the case of the adult. The blood serum of the normal new-born infant protects at a higher concentration and at a constant value, as in the case of the adult. In idiopathic icterus, there is no change in these values. In three cases of pathologic jaundice due to congenital syphilis and in one case of hemorrhagic disease of the new-born, there was no change in these values.

AUTHORS' SUMMARY

THE QUANTITATIVE DETERMINATION OF ALANINE AND PYRUVIC ACID IN
BIOLOGIC SUBSTRATES A I KENDALL and T E FRIEDEMANN, J Infect
Dis 47 171 1930

In concentrations of from 10 to 50 mg, alanine is changed quantitatively to lactic acid in accordance with the equation $\text{CH}_3\text{CHNH}_2\text{COOH} + \text{HONO} = \text{CH}_3\text{CHOH}$

$\text{COOH} + \text{N}_2 + \text{H}_2\text{O}$ Sodium nitrite and either dilute hydrochloric acid, or, better, sodium bisulphate are the reagents used. At the end of the reaction, which requires fifteen minutes at 100 C (212 F) the excess of nitrous acid is removed by urea. After cooling, the solution is made up to a definite volume, and the resulting lactic acid is determined in duplicate on aliquots, using the procedure of Friedemann and Kendall. The precision of the method lies between 97 and 98 per cent for the quantities mentioned. When the alanine content is reduced to 1 or 2 mg, the yield decreases to about from 92 to 93 per cent. The article itself should be consulted for intimate details, and for the applicability of the method to biologic substrates. The precision of this procedure and that for pyruvic acid is brought out in studies of 'resting' bacteria (*J Infect Dis* **47** 186-248, 1930).

Pyruvic acid is reduced to lactic acid in the presence of zinc dust, and NaHSO_4 , with a drop of 20 per cent CuSO_4 to hasten the reaction, in accordance with the reaction $\text{CH}_3\text{COCOOH} + \text{H}_2 = \text{CH}_3\text{CHOHCOOH}$. The quantitative conversion of pyruvic to lactic acid requires two hours' exposure to 100 C. On account of the slight volatility of pyruvic acid, the solution is made faintly alkaline while it is being brought to the reaction temperature. Then the Zn and NaHSO_4 are added. In the absence of certain conflicting substances, the solution, after cooling, is brought to the proper volume, and lactic acid is determined in suitable aliquots, the Friedmann-Kendall procedure being used. In the presence of conflicting substances, which are discussed in detail, precipitation with Cu-Ca is practiced before the cooled solution is made to volume and filtered. Here lactic acid is determined on aliquots of the filtrates. If the details are faithfully followed, the yield is uniformly from 93 to 94.5 per cent. The loss from theoretical yield appears to be due to slight volatility of pyruvic acid. This loss, however, is consistent if the details are rigorously followed.

AUTHORS' SUMMARY

THE INFLUENCE OF ARSENICALS AND CRYSTALLINE GLUTATHIONE ON THE OXYGEN CONSUMPTION OF TISSUES. CARL VOECTLIN, SANFORD M. ROSENTHAL and J. M. JOHNSON, *Pub Health Rep* **46** 339, 1931.

The addition of crystalline SH glutathione to kidney, liver, testis, the Jensen rat sarcoma and baker's yeast does not increase the rate of oxygen consumption beyond the extra amount of oxygen required to oxidize the sulphur of the added glutathione. Oxidized glutathione has no accelerating influence on the oxygen consumption of kidney and testis.

Arsenious oxides (RAsO) in relatively low concentrations cause a pronounced reduction in the rate of oxygen consumption. The pentavalent arsenicals (RAsO_3H_2), including trypanamide, in the same concentrations are devoid of any influence on the oxygen consumption. Of the arsenobenzene derivatives ($\text{RAs} = \text{AsR}$), sulpharsphenamine is ineffective, whereas neoarsphenamine due to its rapid oxidation reduces the oxygen consumption, but less markedly than arsenoxide. These results are in harmony with observations concerning the pharmacologic and chemotherapeutic properties of these compounds, which distinguish the three groups, RAsO , RAsO_3H_2 and $\text{RAs} = \text{AsR}$.

SH glutathione, when added to tissues in the ratio of 10 mols to 1 mol of arsenoxide, prevents the reduction in oxygen consumption caused by arsenoxide alone. S-S glutathione is ineffective, showing that the action of SH glutathione is due to its SH group.

Ferrous ammonium sulphate is ineffective in overcoming the reduction in oxygen consumption produced by arsenoxide.

These observations add further evidence in favor of the theory that the pharmacologic action of these arsenicals is essentially due to a chemical reaction with SH glutathione and possibly other SH compounds of protoplasm.

From the physiologic point of view, the results appear to indicate that glutathione in some as yet unexplained manner is concerned in the oxygen consumption of tissues in vitro.

AUTHORS' SUMMARY

THE RELATIVE AMOUNTS OF LYSOZYME IN THE TISSUES OF SOME MAMMALS
HOWARD FIOREY, Brit J Exper Path **11** 251, 1930

Titration of lysozyme of various tissues of six mammalian species are given. Some results support the idea of lysozyme being primarily an antibacterial agent, other results are difficult to interpret on this basis.

AUTHOR'S SUMMARY

THE PATHOLOGICAL ACTION OF LIGHT A GOODMAN LEVY, J Path & Bact
33 1003, 1930

The epithelial changes (namely hypertrophy of the stratum malpighii and infiltration of the stratum corneum) which were found to occur at the margin of tissue necrosed through the action of ultraviolet light, are found to be common to other forms of injury. They are evidently connected with the processes of regeneration and repair. The hypertrophy of the stratum malpighii is preparatory to the propagation of a strand of flattened epithelial cells over a denuded surface, but may suffice to fit a small gap without this propagation. The spread of infiltrated stratum corneum appears to serve as a protection to an important point of regeneration. These same epithelial changes can be induced through the mitigated action of ultraviolet light, without visible evidence of destruction of tissues, and a similar result is obtained through the mitigated action of some other traumatic agents. An inference that reparative changes are induced by the mitigated action of agents at the margins of an area of intense action cannot, however, be substantiated. A suggestion that these reparative changes may be induced by a diffusible substance emanating from injured or dead tissue, is discussed.

AUTHOR'S SUMMARY

ANOTHER METHOD FOR THE QUANTITATIVE ESTIMATION OF GLYCURONIC ACID
IN THE URINE J SAUER, Klin Wchnschr **9** 2350, 1930

Glycuronic acid determined as carbon dioxide is the basis of this method. According to Sauer, the average daily excretion of glycuronic acid in the urine as estimated by this method is from 0.22 to 0.28 Gm.

EDWIN F. HIRSCH

THE QUANTITATIVE ESTIMATION OF THE GLYCURONIC ACID OF THE URINE
AS A FUNCTIONAL TEST OF THE LIVER J SAUER, Klin Wchnschr **9** 2351
1930

A daily excretion of glycuronic acid in the urine of less than 0.2 Gm. indicates injury of the liver.

AUTHOR'S SUMMARY

Microbiology and Parasitology

CHICKENPOX WITH A BLOOD PICTURE SIMULATING THAT IN LEUKEMIA DOUGLAS GOLDMAN, Am J Dis Child **40** 1282, 1930

An unusual case of varicella with observations on the blood suggestive of leukemia is described. Attempts to cause a similar blood reaction in this case by vaccination and by the injection of typhoid vaccine were unsuccessful. The literature contains no report of similar observations in varicella.

AUTHOR'S SUMMARY

THE VIRULENCE OF *ENTAMOEBAS HISTOLYTICA* L. R. CLEVELAND and ELIZABETH P. SANDERS, Am J Hyg **12** 569, 1930

A pure line and several strains of *Entamoeba histolytica* used were best grown on a new medium comprised of liver infusion agar slants covered with fresh sterile horse serum-saline 1:6, and a small amount of sterile rice flour added to

each tube Amebic abscesses can be produced in the liver by direct inoculation Amebas from acute cases of dysentery grown in the foregoing medium for a year practically lost their ability to maintain themselves in the liver and intestines If they were passed through the liver by inoculation, there was a successive rise in infectivity, from 20 per cent in the first passage to 73 per cent in the sixth passage Not considering the bacteria associated with them there is an increase of the virulence of the amebas with successive passage At the fifth passage through the liver bacteria accompanying the amebas were cultured and injected alone into the liver of nine cats The resulting occurrence of abscesses was higher than in the other sixth passages with which amebas were associated Hence it appears that the bacteria rather than the amebas have gained in virulence Following the second passage through the liver, amebas were freed of associated bacteria, then contaminated with nonpathogenic bacteria These were injected into nineteen animals, and no hepatic abscesses resulted Likewise, none of the bacteria-free amebas produced abscesses when injected alone The generalization that bacteria-free amebas will not produce abscesses cannot be made until more virulent amebas have been used No increase in virulence is noted in the amebas from acute cases of dysentery, in intestinal passage, if they are not grown on mediums Amebic abscesses were found to develop as rapidly in the livers of adult cats as in kittens *E histolytica* cultivated from acute cases of dysentery were more infectious for the liver than for the intestines Amebas from carriers that have not had dysentery and from monkeys are less pathogenic than those from acute cases of dysentery, even when the latter have been cultivated for a year or more and have not been inoculated into animals Attempts to produce abscesses of the brain in guinea-pigs, rabbits and kittens failed Direct injection into the mesenteric veins of cats failed to produce hepatic abscesses and hepatic abscesses failed to follow direct implantation in nine monkeys, sixteen rats and seven rabbits

P H GUINAND

THE CELLULAR REACTIONS TO PRIMARY INFECTION AND REINFECTION WITH THE TUBERCLE BACILLUS LEROY U GARDNER, *Am Rev Tuberc* **22** 379, 1930

Five phases of the reaction to a primary infection in the peritoneal cavity of the guinea-pig are discernible (1) nonspecific inflammation, characterized by a high leukocytosis of from two to three days' duration, (2) focal proliferation, characterized by rapidly increasing mononucleosis, from four to six days in duration, (3) the formation of tubercles, characterized by a high mononucleosis and the appearance of epithelioid cells, from six to eight days in duration, (4) hypersensitiveness, characterized by a high lymphocytosis which developed suddenly a few days before the manifestation of hypersensitiveness of the skin, lasting until shortly before the death of the animal, (5) anergy, characterized by irregular vacillations in the lymphocyte-monocyte ratio and by decreasing hypersensitiveness of the skin Subcutaneous infection with tubercle bacilli in distant parts of the body produces changes in the peritoneal fluid, analogous to, but not so well marked as those due to local infection Reinfection in the peritoneal cavity of animals previously sensitized by subcutaneous inoculation is met by the same type of cellular reactions as those found in primary infections of normal guinea-pigs The most striking variation observed between the reaction to primary infection and reinfection is the accelerated development of a lymphocytosis in the latter Lymphocytosis in the peritoneal exudate has been found to develop coincident with hypersensitiveness of the skin Its degree varies directly with the intensity of the reaction of the skin A lymphocytosis is present in the peritoneal fluid of about 35 per cent of apparently normal guinea-pigs, possibly a manifestation of allergy to chronic or healed nontuberculous infections It is concluded that the lymphocytosis is a result rather than a cause of the changes in the immunologic state It is believed that the clasmatocyte and the monocyte of Sabin's classification are one and the same type of cells and that the morphologic characteristics of the cell vary with its state of physiologic activity

H J CORPHER

BACILLUS NECROPHORUS OBTAINED FROM COWS M L ORCUTT, J Bact
20 343, 1930

Ten strains of *Bacillus necrophorus* isolated from cows have been described. With the exception of one strain, these strains are similar in morphology, in most cultural reactions and in pathogenicity for rabbits. When the strains were compared as to agglutination reactions certain differences were readily apparent, since immune serums prepared with four different strains allowed varying degrees of cross-agglutination and apparently no cross-absorption of specific agglutinins. Each immunizing strain apparently produces specific agglutinins, since they are not absorbed by any other culture. Also, as found in the case of the A culture, a strain may stimulate the production of distinct heterologous agglutinins. The fluffy type of colony usually found by other workers has not been observed with these strains, which in all cases form smooth, even, compact colonies in serum agar shake cultures.

FROM AUTHOR'S SUMMARY

ETIOLOGY OF SPONTANEOUS PULMONARY DISEASE IN THE ALBINO RAT D T
SMITH, N BETHUNE and J L WILSON, J Bact 20 361, 1930

A number of different types of organisms are capable of producing pulmonary infections in the albino rat, such as *Bacillus actinoides*, *B. bronchisepticus*, *B. muni* and a streptothrix. In a group of sixteen rats that we studied there were present (1) an unidentified anaerobic coccus, in all cases, (2) an unidentified aerobic gram-negative bacillus, associated with the coccus, in fourteen cases, (3) *B. bronchisepticus* associated with the coccus in two cases, and (4) a large fusiform bacillus associated with the coccus in two cases, which morphologically was identical with Vincent's fusiform bacillus, found in abscesses of the lung in man. A symbiosis of the unidentified coccus and the unidentified bacillus was demonstrated by our failure to produce the disease by inoculation of pure cultures of either, while the combined pure cultures produced a lesion identical with that of the spontaneous disease. In experiments with tubercle bacilli in albino rats, care should be taken to exclude the possibility of the presence of a coexisting or preexisting spontaneous pulmonary disease in which the tubercle bacillus may be implanted.

FROM AUTHOR'S SUMMARY

STUDIES ON TYPHUS FEVER HANS ZINSSER and M RUIZ CASTANEDA, J Exper
Med 52 649 and 661, 1930

We have adduced strong evidence in favor of identifying the virus of Mexican typhus fever with *Rickettsiae*, or Mooser bodies, observed in the tunica lesions of guinea-pigs with Mexican typhus. Were it not for the possible presence of a few remaining cell fragments in the washings, we would consider this evidence crucial proof.

Our experiments have shown that the Mooser bodies or *Rickettsiae* derived from guinea-pigs with Mexican typhus fever can survive in bedbugs after intra-coelomic injection for ten days remaining capable of infection. We have also succeeded in similarly infecting bedbugs by allowing them to feed on benzolized rats in whose blood *Rickettsiae* had been shown to be present. Injection of the organs of such bedbugs five days after the last and nine days after the first infectious feeding, into guinea-pigs produced typical Mexican typhus fever. Some of the guinea-pigs infected with such bedbug organs and passing through a typical typhus proved to be immune to subsequent inoculation with the European disease. Attempts to infect normal guinea-pigs by allowing infected bedbugs to feed on them or by rubbing the feces into the uninjured skin have, so far, been unsuccessful. We have not, therefore, completed the cycle proving that bedbugs can transmit the disease but we have shown that this is a possibility when dealing with man, obviously more susceptible to the disease than any of our experimental animals. The ease with which *Rickettsiae* seem to survive in the bedbugs suggests the desir-

ability of investigating other common insects for a similar capacity of harboring the typhus *Rickettsiae*—experiments which we have not yet had the time to carry out

AUTHORS' SUMMARIES

STUDIES ON THE COMMON COLD A R DOCHEZ, G S SHIBLEY and K C MILLS, J Exper Med **52** 701, 1930

Chimpanzees are highly suitable animals for the experimental study of human upper respiratory infections. Human colds have been successfully transmitted to apes and human volunteers in 44 per cent of instances tried by means of filtered nasal washings obtained from colds. Certain types of infectious colds are caused by a filtrable agent.

AUTHORS' SUMMARY

THE KILLING OF COLON BACILLI BY X-RAYS OF DIFFERENT WAVE-LENGTHS RALPH W G WICKOFF, J Exper Med **52** 769, 1930

X-ray beams of wave lengths lying in the range between 4A and 0.5 A kill *B. coli* in a semilogarithmically linear fashion. Interpreted in terms of the known quantized absorption of x-rays, this means that one absorption of any of these radiations is sufficient to kill. Though death results from a single absorption, only about one hit in four with Ag K and one in sixty with Ag L radiation is deadly. The course of curves constructed from these experimental results suggests that the portion of this bacterium which is essential to its continued life has a total of approximately 0.01 of the cell volume. For copper and harder radiations the biologic action of the rays is proportional to their measured ionization of air. The same biologic change with the softer chromium K and silver L x-rays seems to require a somewhat more intensely ionizing beam.

AUTHOR'S SUMMARY

THE PRODUCTION OF S FROM R FORMS OF *B. DYSENTERIAE*, SONNE S A KOSER and N C STYRON, J Infect Dis **47** 443, 1930

Smooth forms could be produced from rough forms fairly regularly by successive transfers in dextrose broth at 37 C made daily or twice daily. In some cases, the reversion appeared to be complete, and the R forms totally disappeared. Daily transfers of the R form on nutrient agar slants at 37 C resulted in a slower appearance of S colonies. The R type never completely disappeared in this series of tests. R cultures held on agar slants at room temperature were much more stable. The S-like cultures derived from R forms showed some tendency to spontaneous clumping in 0.85 per cent salt solution. However, in all other respects studied, their deportment resembled very closely that of the parent S strain from which they had been originally obtained.

AUTHORS' SUMMARY

DISSOCIATION OF *B. DYSENTERIAE*, SONNE, AS INFLUENCED BY VARIATIONS IN CULTURE MEDIUM S A KOSER and N C STYRON, J Infect Dis **47** 453, 1930

Smooth forms of three strains of *B. dysenteriae*, Sonne, were inoculated into various liquid mediums. The cultures were aged at 37 C for several months and were plated at intervals on nutrient agar. Variants (intermediate I, rough R and others) appeared with irregularity even in repeated tests with the same strains and conditions. Five and 10 per cent solutions of peptone (Bacto) were most effective in producing colony variation. Higher and lower percentages produced little change. While nutrient broth showed some variation in colony form, the changes were not as pronounced as in the 5 per cent peptone. The sediment was found to contain more I and R colonies than the whole cultures. A variation in dissociative stimulus was found in seven brands of commercial peptone tested. The neutral or alkaline solutions of peptone caused a greater dissociative change.

than acid solutions. Cultures in a 3 per cent meat extract showed colony changes while those in 0.3 and 1 per cent did not. Cultures in 5 per cent bile showed little colony variation. Ten per cent homologous serum had no effect on the S to R change. Aging of S cultures never yielded 100 per cent R type growth. Intermediate and S forms were always present in small numbers. The appearance of I and R types in a culture was often followed by an apparent reversion toward the smooth after prolonged incubation. Morphologically, the R and S were alike. A small variant, not S, R or I, found occasionally was composed of long filamentous forms. Fermentation reactions showed no distinction between the types and little difference in virulence was found. The R form differed in colony appearance, granular growth in broth and spontaneous agglutination in 0.85 per cent salt solution.

EDNA DEIVES

A TYPHUS VIRUS FROM FLEAS ON WILD RATS. R. E. DYER, A. RUMREICH and L. F. BADGER, Pub. Health Rep. **46** 334, 1931

Inoculation into guinea-pigs of fleas removed from rats that had been trapped at a typhus focus resulted in the establishment of a strain of virus that produced a typhus-like reaction in guinea-pigs. Monkeys and rabbits developed agglutinins for *B. proteus* X₁₀ (type O) following inoculation with this strain of virus. Guinea-pigs that had recovered from an attack of endemic typhus produced by the Wilmington strain of virus were apparently immune to a subsequent inoculation with the strain of virus recovered from the fleas.

AUTHORS' SUMMARY

ENZOOTIC EXPERIMENTAL ENCEPHALOMYELITIS (BORNA'S DISEASE). S. NICOLAU and I. A. GALLOWAY, Ann. de l'Inst. Pasteur **45** 457, 1930

Macacus rhesus, inoculated subdurally, dies in a regular period, although initial symptoms vary in the time of their appearance. Chickens and cats are refractory. Cerebral injection of guinea-pigs is followed by death more than a year later. The virus may survive up to 158 days in the brain of the dog, without symptoms. Rabbits may be infected intramuscularly and perhaps by contact, infection by way of the intestines is exceptional, and by way of the popliteal or inguinal lymph nodes does not occur. In the rabbit, "autosterilizing nerve infections" are encountered, generally ending in immunity, less often in death. This may be only apparent, in other neurotropic viruses there may be a dissimulation of the virus by coexistent antibodies, thus rendering demonstration of the virus difficult. Joest-Degen inclusion bodies are frequently noted in autosterilized nerve tissue in fatal or nonfatal cases, often apparently being resorbed. In the brain of rabbits in fatal cases, the microglia play a role in the lesions as shown by hypertrophy, hyperplasia, mobilization and metamorphosis. Modifications of the mesoglia are more intense than in other neurotropic virus infections, the period of infection being longer. Immunization with fresh virus is difficult. Formaldehyzed virus in the muscles or brain immunizes irregularly. A firm immunity follows the intramuscular injection of 1 cc of phenolized glycerin suspension held at 26°C for seven to nine days. Virucidal antibodies were noted in the brain and suprarenal capsules of immunized rabbits, but not in the serum. Complement-fixing antibodies could be demonstrated in the brain, suprarenal capsule, testicles, ovaries and liver. Reactions in a lesser degree are also given by herpes, rabies and other antigens. Equine, bovine and ovine strains of virus are considered identical on immunologic grounds. No cross-immunity exists between Borna's disease and poliomyelitis.

FROM THE AUTHORS' CONCLUSIONS

HEMORRHAGIC LESIONS PRODUCED BY *CLOSTRIDIUM WELCHII*. M. WEINBERG and N. COMBESCO, Ann. de l'Inst. Pasteur **45** 547, 1930

In an article of thirty-four pages, including complete protocols of guinea-pig experiments and illustrations of sections, the authors present conclusions of which the following is a summary. Some lesions are due to a hemolysin, some to a

nonhemolytic toxin and others due to a disturbance of pressure in the vascular system, either healthy or attacked by the necrotizing toxin of this organism. The hemolysis provokes a violent hemoglobinuria. The course of the pigment is traced. Hemoglobinuria is usually followed by hematuria. Renal tissue contains numerous hemorrhagic foci. To the hemolytic toxin is ascribed the red tint of the gelatinous edema found in guinea-pigs, as well as in other cellular tissue. In the kidney and liver are found necrotic lesions caused by the nonhemolytic toxin of *C welchii*. Fatty degeneration of the liver may be produced. Hemorrhagic and necrotic lesions are not encountered. The quantity of toxin plays an important role. The cellular resistance thus results in these variations. Histologic study indicates that there is not always a parallel between intensity of congestion of organs and their pigmentation, in accord with the hypothesis that two toxins exist, one active on blood vessels, one on erythrocytes. Not only hemoglobinuria and hematuria, but hemoptysis, gastro-intestinal hemorrhages and uterine hemorrhages described in patients should be ascribed to the action of the toxin of *C welchii*.

M. S. MARSHALL

ABSORPTION PER OS OF NONPATHOGENIC ACID-FAST ORGANISMS P. NELIS,
Ann de l'Inst. Pasteur **45** 581, 1930

Absorption of nonpathogenic acid-fast bacilli, of the grass bacillus group, via the gastro-intestinal mucosa in the guinea-pig and adult rabbit is not intense and is irregularly effected. On the other hand, in the guinea-pig and the new-born rabbit this absorption is more rapid, more constant and in greater degree.

AUTHOR'S CONCLUSIONS

NEW RESEARCHES ON THE ETIOLOGY OF TRACHOMA U. LUMBROSO, Arch. Inst.
Pasteur de Tunis **19** 280, 1930

Lumbroso succeeded in isolating an organism similar to *Bacterium granulosis* in five of seven untreated, early cases of trachoma. He made injections of a mixture of the five cultures into the conjunctivae of three monkeys (all he could find without natural granulations), a callithrix, a patas (both of which are known to be insusceptible) and an Algerian magot (which is highly susceptible). The last named developed generalized lesions over the whole conjunctiva, and at the time of writing these were still persisting (four months), having diminished but slightly in size and number. The conjunctiva was slightly hyperemic and edematous. The author's impression is rather favorable, but the single result does not permit him to speak categorically.

Lumbroso suggests that some of the inoculations adjudged by Noguchi to be positive were really manifestations of spontaneous granular conjunctivitis. He refers particularly to the experiments on *Macacus rhesus*. According to Noguchi's protocols, the lesions observed on a number of these monkeys were not characteristic since they were for the most part too transient; the duration in most cases was not more than three or four months. True trachomatous lesions last quite a long time.

In order to demonstrate the trachomatous nature of these lesions, Noguchi brings to his support a comparison of the histologic lesions seen in the human conjunctiva after natural trachomatous infection, and experimental lesions, obtained by the injection of *Bact. granulosis*. The study of these lesions having shown him a similar histology, he concludes that *Bact. granulosis* is the etiologic agent of trachoma. This conclusion is not warranted, since "from the histologic and cytologic points of view one does not see in the beginning of the infection any characteristic that would permit of a differentiation between the follicles of trachomatous granulations and those of other analogous lesions. The situation is quite different in the advanced stage, when degeneration of the follicles has taken place and cicatricial tissue begins to appear."

CHARLES WEISS

EXPERIMENTAL POLIOMYELITIS FROM INOCULATION INTO THE SCIATIC NERVE
E WESLON HURST, J Path & Bact **33** 1133, 1930

The course of poliomyelitis following intrasciatic inoculation is described. The order of appearance of virus and lesions in the various regions of the central nervous system accords with the view already expressed that the axons are the main transmitting structures in the disease. The cerebrospinal fluid plays a subsidiary part in the dissemination of the virus, which may on occasion be detected in the fluid.

AUTHOR'S SUMMARY

TYPES OF TUBERCLE BACILLI IN THE SPUTUM A S GRIFFITH, J Path & Bact
33 1145, 1930

In the examination of the sputum in 926 cases of phthisis pulmonalis in foreign countries none has been found due to the bovine tubercle bacilli, in England, 3 of 327 patients have been found to be expectorating bovine tubercle bacilli, in Scotland, 18 cases in 468 patients have been reported. In one case the bovine organisms were mixed with human tubercle bacilli, but the remainder gave pure cultures of bovine tubercle bacilli. In the majority of bovine cases, the histories indicated that the tubercle bacilli entered the body through the alimentary tract. Two autopsies showed cavities in the lungs from which pure cultures of bovine tubercle bacilli were obtained. In 4 of 6 autopsies the anatomic observations indicated the alimentary tract as the portal of entry. In the remaining 2 cases the evidence was inconclusive, but favored the alimentary tract rather than the respiratory tract. Investigations have shown that ulcerative pulmonary tuberculosis in man may be caused by bovine tubercle bacilli which invade the body through the alimentary tract. In none of the cases was there a family history of tuberculosis and no evidence that the infection was directly from a previous case of phthisis. No evidence has been obtained of the occurrence of pulmonary tuberculosis in any of the contacts of bovine cases, but instances of fatal generalized tuberculosis in children in whom the portal of entry was the respiratory tract are given.

E DELVES

ON THE PATHOGENICITY OF THE BACILLUS CALMETTE-GUERIN MOTI MAL-
KANI, Tubercle **11** 433, 1930

Although much attenuated, BCG still shows virulence. It produces specific tuberculous lesions when inoculated into guinea-pigs and rabbits, and, depending on the degree of resistance it meets within the animal organism, it either disappears from the system or leads to a process which, in some cases, terminates fatally.

H J CORPER

EFFECT OF CALCIUM ON ANTHRAX CULTURES J BORDET and E RENAUX, Ann
de l'Inst Pasteur **45** 1, 1930

Dissociated S and R types of anthrax cultures, sporogenous or asporogenous, or mixtures, occurred frequently on ordinary agar mediums. After serial transfer, a marked difference was secured in ovalate (sodium) medium (almost wholly spores) and on calcium (chloride) medium (persistent, vegetative, filamentous stage). The variants in ovalate medium the authors subdivide into types A (and AA) and B. Colonies of type A are more numerous, they are flat, dull and rough, frostlike on transmitted light, and tend to develop with the formation of a fine ring. Colonies of type B are less numerous, whiter, a little more convex, smoother and less granular. The formation of spores is more marked in type A. Differences in morphology, viscosity and virulence were noted. Eleven figures in color illustrate the morphologic variation.

M S MARSHALL

BIOLOGIC STUDIES ON THE TUBERCLE BACILLUS S A PETROFF, W STEEKEN, JR, and E A SCHNIEDER, Beitr z Klin d Tuberk **74** 499, 1930

The work on dissociation of tubercle bacilli is reported in detail. It is essentially the same work that has been reported in various American publications. So far, definite dissociates, varying considerably in morphology and virulence, have been obtained from bovine and avian bacilli and from the Calmette-Guérin bacilli. The work on the dissociation of the human type is still incomplete.

MAX PINNER

FILTRABLE FORM OF THE TUBERCULOSIS VIRUS O KIRCHNER, Beitr z Klin d Tuberk **74** 521, 1930

Filtrates were made of pure cultures of tubercle bacilli and of tubercle bacilli grown in symbiosis with other organisms. In no case was it possible to demonstrate by cultural methods or by inoculation in animals the presence of filtrable forms. Only one experiment seemed to yield a positive result in an animal, but the interpretation of this result is uncertain.

MAX PINNER

THE FINDING OF SPIROCHETES IN SYPHILITIC MESAORTITIS W BUSZ, Frankfurt Ztschr f Path **40** 139, 1930

The author describes two cases of syphilitic mesaortitis. A man, aged 29, never gave a history of syphilis and was never treated for syphilis. The autopsy revealed syphilitic mesaortitis. A marked chronic defensive reaction was noted throughout the adventitia of the aorta, in addition to an acute inflammatory process. By using the Jahnke stain, many spirochetes could be demonstrated in one circumscribed area of the media. A woman, aged 40, gave a history of syphilis for which she was not treated over a period of thirteen years. In the year preceding death, she had received eight injections of arsphenamine. The injections were interrupted after jaundice developed. The aorta showed deep scars, but hardly any acute reaction in the aortic wall. No typical spirochetes were demonstrable.

The author believes that the spirochetes are carried through the body by means of lymph vessels. In most of the organs, the spirochetes are overpowered by immune bodies. In the brain, spinal cord and media of the aorta, the spirochetes can live for a long period, because these organs are characterized by a slow metabolic rate and are poor in immune bodies. The opinion is expressed that the anatomic process in the aorta might progress even after the spirochetes have disappeared from the aortic wall.

O SAPHIR

THE ETIOLOGY OF FOLLICULAR CONJUNCTIVITIS K LINDER and RIEGER, Klin Monatsbl f Augenh **85** 96, 1930

Of two attempts at transmission of human folliculosis to *Macacus rhesus*, one yielded positive results. In two of four cases of folliculosis, a germ was isolated, which showed a strong resemblance to Noguchi's *Bacillus granulosis*. The first strain unfortunately died, and an inoculation into a macaque resulted negatively. The second strain which could be kept alive only with the greatest difficulty, likewise gave negative results when inoculated into a macaque. But when it was inoculated into the conjunctivae of Dr Lindner, there was observed, after an incubation period of about three weeks, the beginning of follicular changes in the conjunctiva, without remarkable inflammation. Two and one-half months later these lesions had almost disappeared.

CHARLES WEISS

STUDIES IN CELLULAR CHANGES HORATIO GOLDIE, Ztschr f d ges exper Med **72** 598, 1930

The leukocytes of sterile pus are characterized by accelerated oxidation and swelling, leading to cellular autolysis. Failure of resorption causes the ferments in liquid pus to act on the cells. Addition of a catalyzer of oxidation—a small

amount of sterile pus—to normal bacterial colonies causes metabolic changes that are identical with the manifestations of the action of bacteriophage

PEARL ZEEK

EFFECT OF TUBERCULOSIS ON SUBSEQUENT INFECTIONS T HIRAYAMA, Ztschr f Immunitätsforsch u exper Therap **68** 218 and 230, 1930

Tuberculous guinea-pigs and mice are more resistant to streptococci and to anthrax bacilli, than normal control animals

THE VIRULENCE OF THE SALIVA IN HYDROPHOBIA H PALAWANDOW and A I SEREBRENNAJA, Ztschr f Immunitätsforsch u exper Therap **68** 236, 1930

The virus of hydrophobia is present in the saliva in cases of the disease in man

CULTURES OF SPIROCHAETA PALLIDA IN FLUID MEDIUMS F HODER, Ztschr f Immunitätsforsch u exper Therap **68** 256, 1930

In a medium composed of rabbit serum broth and rabbit liver *Spirochaeta pallida* remained alive for several weeks. It is urged that probably contamination at the time of inoculation is the most important cause for failure in cultivating the spirochete

THE VIRULENCE OF TUBERCLE BACILLI IN TUBERCULOSIS IN MAN AND ANIMALS B LANGE, Ztschr f Tuberk **57** 129, 209, 1930

The virulence of tubercle bacilli can be tested by intracutaneous injection of minimal amounts of tubercle bacilli into guinea-pigs of equal body weight, with simultaneous control of the number of bacilli by cultural methods. Strains of low virulence demonstrate a long incubation period, a delayed appearance of the primary lesion in the skin and less advanced lesions in the internal organs after a period of three months. The virulence of bovine bacilli is parallel in mice, rabbits, cattle and sheep. Tubercle bacilli from human lesions show marked differences in virulence. There does not seem to exist any parallelism between the virulence of a strain and the clinical severity of the case from which it is isolated

MAN PINNER

THE FILTRABLE FORM OF THE TUBERCLE BACILLUS J ORSKOV and K A JENSEN, Ztschr f Tuberk **57** 398, 1930

Seventy guinea-pigs were given injections of the filtrates from forty-eight different specimens of tuberculous material. In none of these experiments was it possible to demonstrate a filtrable virus. In one guinea-pig typical generalized tuberculosis developed

MAN PINNER

BACTERICIDAL ACTION OF IODIPIN ON TUBERCLE BACILLI AND OTHER BACTERIA T H ANAKO, Ztschr f Tuberk **58** 178, 1930

Iodized sesame oil (20 per cent) has no demonstrable bactericidal action on tubercle bacilli. Progenic and intestinal organisms are killed by iodized oil only after several hours

MAN PINNER

NONACID-FAST FORMS OF TUBERCLE BACILLI E A SCHNIEDER, Ztschr f Tuberk **58** 247, 1930

Suspensions of tubercle bacilli were filtered and seeded on Petroff's medium. In 15 of 368 seedings, colonies of nonacid-fast forms were observed. With increasing age, few acid-fast granules and acid-fast rods were found in these colonies

MAN PINNER

FILTRABLE MICROBE IN THE BLOOD IN PERNICIOUS ANEMIA AXEL HOLST,
Norsk mag f lægevidensk **92** 1, 1931

In the blood of patients suffering from pernicious anemia according to the clinical diagnosis, Holst finds an extremely minute, filtrable microbe that in solutions of hemoglobin causes destruction of the hemoglobin. Animal experiments of a preliminary nature have not given rise to any disease.

Immunology

IMMUNITY IN EXPERIMENTAL COCCIDIOSIS OF RABBITS GEORGE W. BACHMAN,
Am J Hyg **12** 641, 1930

A study was made of fifty-seven rabbits from a colony shown to be free from the common parasites with the exception of the intestinal coccidia *Eimeria perfolians*. Rabbits from 4 months to 4 years of age that had lived in this colony and had had previous infections with *Eimeria perfolians* were immune to experimental infection with the same organism. Rabbits of the same colony that were immune to infection with *Eimeria perfolians* were not resistant to infection with *Eimeria stiedae*, independent of age. The attempts at active and passive immunization failed to protect rabbits against infection with *Eimeria perfolians*.

AUTHOR'S SUMMARY

PRECIPITIN AND COMPLEMENT-FIXATION TESTS ON DOG SERA WITH ANTIGEN FROM THE DOG HOOKWORM, *ANCYLOSTOMA CANINUM* JOHN E. STUMBERG,
Am J Hyg **12** 657, 1930

Dried filariform larvae and adults of the dog hookworm, *Ancylostoma caninum*, extracted with acid and alkaline saline solutions, were found to be highly antigenic when injected intravenously into rabbits, alkaline saline extracts were preferable to acid. Slight differences between larval and adult antigens were found—mainly the production of a higher titer by the adult extracts—but the two could hardly be considered serologically distinct. The antibodies produced in immunized rabbits were species specific in dilutions of 1:4,000 or over, and group specific in dilutions from 1:1,000 to 1:4,000. Nonspecific reactions were obtained with antigens prepared from other intestinal helminths, but never in dilutions above 1:1,000 and usually only of 1:100. No evidence could be found that the antigenic action was due to contaminating bacteria. The serum of dogs showed a nonspecific complement-fixation titer with these antigens as high as 1:500, and this reaction was not destroyed by heating to 62°C for one-half hour. Dogs given parenteral injections of larval and adult antigens failed to show any precipitins in the serums or any complement-fixation in excess of the nonspecific level. Dogs experimentally infested with hookworms, either by a single infection or after several infections failed to show antibodies in their serums up to seven weeks after infestation.

AUTHOR'S SUMMARY

IMMUNITY AND THE MECHANISM OF SPLENIC CONTROL IN *BARTONELLA* ANEMIA OF RATS WILLIAM W. FORD and CAI ISTA P. ELIOT, Am J Hyg **12** 669, 1930

The normal unsplenectomized rat exhibits a natural resistance to anemia caused by *Bartonella* unrelated to previous contact with the virus. This resistance is broken down as soon as the spleen is removed. Attempts to demonstrate a protective substance in the blood or tissues of normal or of recovered rats have so far proved unsuccessful. It may be suggested that the spleen, by the structural position of its cells, acts as a filter in which the bartonellas are taken out of the circulation and destroyed or inhibited. It may also be indicated that the classification of *Bartonella muris* among pathogenic parasites has never been definitely worked out. Is it possible that they represent some peculiar type of organism?

which finds a favorable location in the spleen for its usual development. When this is removed they may enter on a vegetative phase on the red cells which results in a destruction of these cells and the eventual disappearance of the virus

AUTHORS' SUMMARY

AN EXPLANATION OF THE MECHANISM OF THE WASSERMANN AND PRECIPITATION TEST FOR SYPHILIS HARRY EAGLE, Bull Johns Hopkins Hosp 47 292, 1930

There is not merely a superficial similarity between the flocculation reaction for syphilis and bacterial agglutination by an antiserum, or between the Bordet-Gengou phenomenon (specific complement-fixation) and the Wassermann reaction. The analogy extends to the basic mechanisms of the reactions. Reagin, an altered globulin in syphilitic serum, combines with the colloidal particles of beef heart lipid ("antigen"). The surface film of protein thus formed sensitizes the particles to flocculation by electrolyte (Sachs-Georgi, Kahn and others) and also adsorbs complement (Wassermann). Antibody-globulin affects bacteria, red cells or foreign protein in exactly the same manner. The serum change characteristic of syphilis may therefore well represent an antibody response to products of infection. As will be shown, the fact that lipoids of normal tissue can be used instead of spirochetes as the antigen in the test tube reaction does not exclude this possibility.

AUTHOR'S SUMMARY

PHENOMENA OF LOCAL SKIN REACTIVITY G. SHWARTZMAN, J. Exper Med 52 5, 1931, 1930

The effect of bacterial variation on the local skin reactivity to bacterial filtrates is reported. Stock strains of *B. typhosus* were found to have reacting factors which differed in their neutralizability by antistock serum. A rough variant of the stock strain showed reacting factors of new specificity. Reacting factors of various degrees of neutralizability, with one exception, were produced by strains showing no difference in the appearance of the colony. A parallelism between the degree of agglutinability and the degree of neutralizability was found. Precipitation occurred in mixtures of toxic filtrates and immune serum despite low neutralization. Rough filtrates, nonneutralizable by antistock serum, failed to precipitate the latter, but as neutralizing, antirough antibodies appeared, antirough precipitates developed. The rough strains were less virulent than the stock strains. The filtrates containing rough reacting factors seemed as lethal to mice and rabbits as the filtrates of stock *B. typhosus*.

EDNA DELERS

STUDIES IN THE SEROLOGY OF SYPHILIS HARRY EAGLE, J. Exper Med 52 717, 739 and 747, 1930

Lipoid antigen, when colloidal dispersed in water, forms a relatively stable amphoteric suspension with predominantly hydrophil properties. The protein of normal serum is strongly adsorbed by the lipoid antigen forming a protective film of hydrophil protein around the constituent particles and adding to their stability away from their iso-electric point. Syphilitic serum is more or less irreversibly adsorbed by the lipoid antigen and is not removed by washing. The precipitate in the flocculation test consists of from 80 to 90 per cent of the antigenic lipoid plus some specific component of syphilitic serum with which it has combined. In every positive Wassermann reaction there is a microscopic aggregation of lipoid particles into aggregates. The substance in syphilitic serum responsible for the positive Wassermann reaction, like that which causes positive reactions in flocculation tests, is associated with the globulin factor of the serum. Excess of antigen removes both flocculating and complement-fixing substances completely. The same film of denatured serum globulin that sensitizes the antigen particles also endows them with avidity for complement. Beef heart lipoid antigen

can be substituted for any similarly acting substance, as the peptizing agent Antigen causes the colloidal dispersion of cholesterol by forming a protective film around minute aggregates of cholesterol before they exceed the limits of colloidal stability. The sensitizing effect of cholesterol on the Wassermann antigen is due solely to its effect on the size of the particle. The coarse dispersion of antigen caused by cholesterol facilitates subsequent aggregation.

E. WEISS

THE AGGLUTINATION TEST FOR BRUCELLA ABORTUS B. S. HENRY and J. TRAUM, *J. Infect. Dis.* **47** 367, 1930

In the tube method of testing, formaldehydized antigen has a tendency to intensify or cause proagglutination with human, bovine and porcine serums to such an extent that occasionally strongly positive serums might be missed in routine mass testing. In the same serums tested with phenolized or tricesolized antigen, the interference is absent or reduced to such a point that it is not misleading. Incubation over night at about 37 C and then for twenty-four hours at room temperature gives better results than other methods of holding described in this paper. Variations in the opacity of the antigen within fairly wide limits have no great influence on the correct interpretation of results. A rapid and satisfactory method of reading tests, based on the clearing of the fluid and the manner of the distribution of the agglutinated and nonagglutinated bacteria at the bottom of the tube, is presented.

AUTHORS' SUMMARY

PROPERTIES OF METHYLIC TUBERCULOUS ANTIGEN L. NEGRE and A. BOQUET, *Ann. de l'Inst. Pasteur* **45** 415, 1930

The efficacy of this antigen, considered in a previous paper (*Antigenotherapie de la tuberculose par les extraits methylques de bacilles de Koch*, Paris, Masson & Cie, 1927), is further studied, with some observations on the mechanism of its action. Experimental tuberculosis responds favorably to subcutaneous injections if they are not given too close together and are not repeated oftener than twice a week. Acetone serves best as a solvent for the waxy substances of the organisms that serve in the preparation of the antigen. The methylc antigen combats intoxication in the rabbit following the injection of either dead bacilli or of acetone extracts. The general state of the tuberculous patient is thus improved by an antitoxic action of the lipoids of the bacilli in the antigen. The lymphocyte-monocyte ratio is increased. Massive doses of methylc and ether extracts of organisms treated with acetone, given intravenously or subcutaneously, circumscribe and retard the evolution of the tuberculous process. Acetone extracts cause the reverse. An intense sclerosis of pulmonary lesions is noted in certain cases. A particularly favorable action is apparent in tuberculosis of the ganglions, joints, peritoneum, pleura, eyes and genitalia. In cutaneous tuberculosis, the extracts act on the gum tissue, the ulcerative and vegetating lesions and the papulonecrotic tuberculids. Great service may also be rendered in renal tuberculosis and in pulmonary types in the early and torpid forms, ulcerocaseous and fibrocaceous.

M. S. MARSHALL

BCG FROM LYMPHATIC GANGLIONS OF VACCINATED GUINEA-PIGS E. PIAZECKA-ZEYLAND, *Ann. de l'Inst. Pasteur* **45** 439, 1930

Guinea-pigs were vaccinated with BCG by mouth. In young animals, more surely than in adults the BCG passed the intestinal mucosa and was recovered from the lymphatic ganglions by culture quite regularly between the second and fourth weeks following ingestion of the vaccine, and irregularly up to the tenth week. Although a positive tuberculin test was noted organisms were not recovered after this time.

M. S. MARSHALL

ON THE ADAPTATION OF SPIROCHAETA PALLIDA TO THE BRAIN F GEORGI
and C PRAUSNITZ, Arch f Hyg **103** 173, 1930

Altered antigenicity of *Spirochaeta pallida* grown under different cultural conditions is shown. Stock cultures were grown on ascites agar plus rabbit kidney. Distinct morphologic changes were noted when the cultures were transferred to ascites agar to which rabbit brain had been added. When animals or patients were immunized with altered strains that had been killed by heat or alcohol, the antisera were found to be strain specific by the complement-fixation test. Pseudospecificity was ruled out by control tests. When transferred to brain-free medium, this neurotropism was lost. It was regained in brain medium, however, the change being readily reversible.

EDNA DELVES

COMPLEMENT-FIXATION WITH ALCOHOLIC EXTRACTS OF MENINGOCOCCI H
SACHS, Ztschr f Immunitätsforsch u exper Therap **69** 221, 1930

By washing meningococcus cultures with 80 per cent alcohol, an extract was obtained that fixed the complement in conjunction with antimeningococcus serum. This result is interpreted as indicating that the serum contained "lipoid antibodies."

COMPLEMENT FIXATION AND PRECIPITATION BY ANTIDIPHTHERIA SERUM F
HORING, Ztschr f Immunitätsforsch u exper Therap **69** 244, 1930

Alcoholic extracts of diphtheria bacilli and diphtheria toxin fixed the complement in conjunction with antidiphtheria serum. However, not every serum may be active, even if rich in antitoxin. The complement-fixing property may be removed by treating serum with diphtheria bacilli.

ACTIVATION OF LIPOID ANTIGENS BY CHOLESTERIN G F GAETANI, Ztschr f
Immunitätsforsch u exper Therap **69** 277, 1930

Heterogenetic organ extracts, containing small amounts of lipoids, may acquire the function of heterogenetic antigens in complement-fixation and precipitation by the addition of cholesterol. This effect seems to be due to physiochemical action on the antigen.

CHEMICAL INTERPRETATION OF IMMUNE HEMOLYSIS L JARNO and L SURANYI,
Ztschr f Immunitätsforsch u exper Therap **69** 298, 1930

Both normal and immune amboceptors consist partly of complex amino-acid groups and partly of cholic acid compounds.

Tumors

A PRIMARY MALIGNANT TUMOR OF THE SOLAR PLEXUS F C HELWIG, G H
HOLIE and E L MILIFF, Arch Neurol & Psychiat **25** 162, 1931

The patient, a woman, aged 60, had had pain in the right lower quadrant of the abdomen for about four months, with loss of weight. An exploratory laparotomy revealed a sarcomatous tumor in the retroperitoneum to the right and above the head of the pancreas. The tumor was left untouched. Death followed ten days later. Necropsy revealed an encapsulated tumor, 6 cm in diameter, that apparently originated in the plexuses composing the solar group. It partly surrounded the aorta and extended 3 cm below the bifurcation of the renal arteries. The adjacent lymph glands were not involved. The tumor contained large areas of necrosis and consisted mainly of round and spindle-shaped cells among which small nerve fibers were seen. No definite ganglion cells were seen. Various staining methods were used in apparently unsuccessful attempts properly to classify the tumor which was finally diagnosed as a neurosarcoma.

GEORGE B HASSIN

ORIGIN AND DEVELOPMENT OF GIANT CELLS IN GLIOMAS BERNARD J ALPERS,
Arch Neurol & Psychiat **25** 281, 1931

In spite of the progress made in the study of gliomas by application of the methods of the Spanish school, the significance of certain types of cell groups in gliomas is still obscure, i e., in gliomas in which giant cells predominate and which are often classified as spongioblastomas. Giant cells also occur in astroblastomas and astrocytomas. All of these types of tumors have been studied by Alpers. He gives a detailed description of a spongioblastoma in which the giant cells were especially numerous and situated in the frontal lobe, extending into the corpus callosum. The callosal portion was rich in astroblasts and astrocytes. There were few giant cells in this portion, but they were numerous in the cortex, where they were scattered among smaller, also multinuclear, cells, mostly around blood vessels. Morphologically, some of the cells were young spongioblasts some of which differentiated into early astroblasts. In addition, there were large astrocytes, often true monster cells. The tumor contained numerous nerve fibers, some of which were relatively intact. Neuroglia fibers were also abundant in the astroblastic and astrocytic portions of the tumor. Alpers found the giant cells to arise from amitotic division of the nuclei of gliocytes that failed to become mature and were frustrated, as it were, in their attempt to divide normally. In some cases the amitotic division of the nucleus resulted in the formation of numerous nuclei, as many as twelve in some cells, and in the creation of bizarre form, such as rosetts.

GEORGE B HASSIN

GANGLIOGLIOMA CYRIL B COURVILLE, Arch Neurol & Psychiat **25** 309, 1931

In two cases of ganglioglioma, termed by some investigators ganglioneuroma or ganglionic glioma, reported by Courville (*Arch Neurol & Psychiat* **24** 439, 1930), the tumors occurred in the floor of the third ventricle. The present case was that of a woman aged 35, who died after an illness of about two months' duration. A tumor 2.8 by 2.6 cm was found in the right temporal lobe where it almost completely obliterated the inferior horn. It was sharply delimited from the tissue of the brain and was vascular at the margins. The cells varied in size and shape, their nuclei resembled those of ganglion cells and exhibited typical mitotic figures. Of great interest were the atypical, bizarre forms of cell division, such as constrictions of the nuclei, indentations and buddings. Some cells were identified as typical neuroblasts, others as glia cells. The walls of the blood vessels were hyperplastic.

GEORGE B HASSIN

SKELETAL METASTASES FROM CARCINOMA OF THE RECTUM A H AUFSSES,
Arch Surg **21** 916, 1930

Observations on eight cases of metastasizing carcinoma of the rectum to the skeleton support von Recklinghausen's theory that metastases to bones are due to perivascular stagnation of tumor cells as they pass from the blood vessels outside the bony structure to the vascular bed within the bone, and are not due to primary embolic blocking of the vascular channel in the bone by a mass of neoplastic cells. Blood vessels around the bone are of changeable size. Those within the bone are of fixed caliber. The blood is often carried from a narrow peripheral vessel into a wider channel within the bone marrow. The change in size in the vascular bed tends toward stagnation of embolic tumor cells and favors their multiplication. Metastases to the bones occur in order of frequency in the vertebrae, femur, pelvis, ribs, sternum, humerus, skull, tibia, radius and ulna.

N ENZLER

PROBLEMS OF MELANOMA J EWING, Brit M J **2** 852, 1930

The author states that his object is to enumerate the problems of melanoma, not with the ambition of presenting a solution, but with the hope that a simple

statement of them may lead to a more definite effort toward a solution. He notes the fact that the discovery of the nerve origin of the nevus was made by Soldan in 1899, but remained practically unnoticed until rediscovered and elaborated by Masson in 1927. Whether the nevus cell is neuro-ectodermal or mesoblastic is uncertain.

Cases are seen in which it seems almost certain that the chromatophores in nevi of the nerves develop from nevus cells. This would lend support to the view that the chromatophore is of nerve origin. However, once formed the chromatophore seems to enjoy an independent and separate existence. Whether there are other sources of chromatophores is uncertain, but improbable. The proof that the nevus cell is of nerve origin helps to confirm and explain many clinical and anatomic observations that relate melanoma to neurofibromatosis.

The epithelial theory of the origin of chromatophores has lost support. In the past, confusion has arisen in the fact that certain definitely epithelial tumors have been pigmented. In this case the author believes that the pigment is due to independent chromatophores accompanying the tumor cells, or to the assumption of the production of pigment by the epithelial cells themselves.

ROY F. FLEEMSTER

ON THE POSSIBILITY OF TRANSMITTING MAMMALIAN NEOPLASMS WITHOUT THE INTERVENTION OF LIVING CELLS. W. CRAMER, Ninth Sc. Rep. on Investigations of Imp. Cancer Research Fund, 1930, p. 22

The application of repeated freezing and thawing to transplantable tumors of the mouse and rat reveals a difference between carcinomas and sarcomas. The subcutaneous inoculation of frozen carcinoma cells is always negative, while that of frozen sarcoma cells may give rise to new tumors. Different sarcoma strains vary in the extent to which freezing affects their transmissibility. In two of the three strains examined it was rare to obtain tumors by the inoculation of frozen material. In the third tumor it was of frequent occurrence. There are further variations in this same sarcoma strain in the course of its propagation, at one time freezing may completely abolish the transmissibility, at another time 100 per cent of positive results may be obtained by the inoculation of frozen material. Frozen sarcoma tissue, which on inoculation produces tumors in a high percentage, rapidly loses this power by incubation or by repeated washing with saline. It has not been possible to cultivate cells *in vitro* from material that has been subjected to repeated freezing and thawing. This is also true of normal cells, carcinoma cells and sarcoma cells. It is safe to conclude from the results that carcinoma cells are killed by repeated freezing, behaving in this respect like normal cells. It can also be concluded that the cells of different sarcoma strains show biologic differences when tested in this way, and that such differences are exhibited even by cells of the same sarcoma strain (37 S) when tested at different times. Whether these differences must be interpreted as variations in the resistance of the cells to death by freezing or as indicating the possibility of transmitting mammalian malignant neoplasms without the intervention of living cells cannot be decided conclusively on the basis of the evidence available at present. It is pointed out, however, that the experimental evidence of previous workers so far as it is based almost entirely on negative results with cell-free material obtained from mammalian carcinoma cells, is not as conclusive for the absence of an agent separable from the living tumor cell as has hitherto been supposed.

AUTHORS SUMMARY

ON THE TRANSMISSION OF THE ROUS SARCOMA NO. 1 OF THE FOWL BY FROZEN MATERIAL. W. CRAMER and L. FOULDS, Ninth Sc. Rep. on Investigations of Imp. Cancer Research Fund, 1930, p. 33

The experiments present a complete series of phases in the life cycle of the Rous tumor no. 1. In one phase, which is most commonly seen, it is readily

transmissible without living cells and is therefore presumed to contain a highly virulent agent in a relatively high degree of concentration. In another phase it cannot be transmitted without living cells, even when loss of the agent by incomplete extraction and retention by the filter candle is excluded by the device of using frozen material for inoculation. Therefore, in that phase the Rous sarcoma no 1 behaves like a mammalian neoplasm. The negative results obtained with the frozen material in that phase prove that the process of repeated freezing and thawing adopted in these experiments is capable of killing all of the sarcoma cells. Between these two extremes there are all degrees of transition represented by attenuation or diminished concentration of the agent. The observation that in these phases of transition inoculation of the frozen material gives better results than inoculation of the filtrate is an indication of the fact mentioned, that the preparation of a filtrate necessarily involves a loss of the "agent" partly by incomplete extraction and partly owing to a partial retention of the agent by the filter candle. The extent of this loss, as demonstrated by these experiments is considerable, and is greater than is at present realized. This lends support to the view expressed in the preceding paper, that the failure to transmit a malignant new growth by a filtrable extract cannot be accepted as conclusive proof of the absence of an "agent." Transmissibility by cell-free material, from whatever point of view it may be regarded, can no longer be considered a fundamental distinction between mammalian sarcomas and the so-called "filtrable" tumors of the fowl. The experimental results recorded in this and the preceding paper, therefore, tend to approximate the filtrable tumors of the fowl to the mammalian sarcoma. Even if one considers the actual results, without making any attempt to interpret them or to discuss their possible theoretical significance, a clear analogy is established between the mammalian sarcomas and the Rous tumor no 1 of the fowl. With both groups the inoculation of frozen material gives at one time positive results, at another time negative results. The difference between these two groups of tumors is only one of degree: in the Rous sarcoma the positive results are the rule, while negative results are rare, for mammalian sarcomas, the reverse is true.

AUTHORS' SUMMARY

TAR-CANCER INDUCTION IN MICE WITH SPONTANEOUS MALIGNANT NEW GROWTHS. J. A. MURRAY, Ninth Sc Rep on Investigations of Imp Cancer Research Fund, 1930, p. 83

No clear evidence of resistance to the induction of cancer by tar was obtained in sixty-one mice with spontaneous mammary cancer and in two mice with previous cancer caused by tar. No significant differences were noted whether recurrence took place or not. The result is provisionally attributed to the use of an active preparation in the testing course of tar painting so that the differences between the three series of animals were obliterated.

AUTHOR'S SUMMARY

NERVES AND CANCER. R. J. LUDFORD, Ninth Sc Rep on Investigations of Imp Cancer Research Fund, 1930, p. 99

Throughout this investigation no indication has been found of the existence of a specific innervation of cancerous growths. The occasional presence of nerves in cancer is due, either to the persistence of pre-existing nerves, or more usually to nerves becoming included within the cancer owing to the invasive character of its growth. Regeneration following injury to such nerves may give a false impression of actual innervation. It is concluded, therefore, that the growth of a malignant tumor is independent of any specific organization of nerves.

AUTHOR'S SUMMARY

EXPERIMENTAL REPRODUCTION OF RECLUS' DISEASE OF THE MAMMARY GLAND
IN MICE N GOORMAGHTIGH and A AMERLINCK, Bull Assoc franç p
l'étude du cancer **19** 527, 1930

The authors were able to reproduce a marked hyperplasia of the glandular structure of the breast in mice by daily injections of a lipoid-free folliculin. They affirm that this substance is largely responsible for the albuminous secretions that characterize the early stages of the disease. The hormone of the corpus luteum is thus responsible for the hyperplastic aspect of the disease. The disease could not be reproduced in castrated mice or in those with hypoplastic ovaries deprived of the cycle and therefore of the periodic action of the corpus luteum. They believe that cystic degeneration of the breast results from the combined and alternating action of two ovarian hormones secreted in doses exceeding the normal during a disturbed ovarian cycle when the luteinic phase is prolonged.

B M FRIED

METASTASIS OF PROSTATIC EPITHELIOMA INTO A GIANT CELL SARCOMA OF
THE MESENTERY C SIMARD and J SAUCIER, Bull Assoc franç p l'étude
du cancer **19** 544, 1930

The authors report a case, and present two demonstrative plates.

B M FRIED

SUBUNGUAL MELANOMAS AND THEIR DIFFERENTIAL DIAGNOSIS F E ADAIR
and G T PACK, Bull Assoc franç p l'étude du cancer **19** 549, 1930

The bed of the nail is rarely the seat of a melanoma. The thumb and the toe are more frequently affected. As a rule, the tumor metastasizes, by way of the lymphatics. It grows more slowly and is relatively less malignant than the same type of tumor found in other organs. The differential diagnosis lies between paronychia, pyogenic granuloma, onychomycosis, syphilitic chancre, Dupuytren's contracture, subungual hematoma, fibroma, angiosarcoma and epithelioma.

B M FRIED

PRIMARY CARCINOMA OF THE LIVER ENRICO PUCCINELLI, Arch ital di anat
e istol pat **1** 781, 1930

A case is described in a man, aged 53, the clinical diagnosis was sarcoma with multiple metastases. Postmortem examination showed a greatly enlarged liver covered with yellowish-green nodules. There were also a few nodules on the walls of the gallbladder. There were soft, yellowish swellings connected with the first and eighth ribs. Histologically, the nodules of the liver and of the bone were of identical structure, consisting of polygonal cells resembling those of the liver, arranged in trabeculae and tubules and containing pigment similar to biliary pigment. The author therefore believes that the case was one of primary carcinoma of the liver with metastases in the skeletal system.

E WEISS

HEALING OF CARCINOMATOUS METASTASES IN BONE J ERDHEIM, Virchows
Arch f path Anat **275** 383, 1930

The healing of carcinomatous metastases in bone, when associated with marked new formation of osseous tissue, was first thoroughly studied by von Recklinghausen and has received attention from other pathologists since his time. The healing of osteoclastic metastases has, on the other hand, according to Erdheim, received scant attention. He cites several instances in which the bony union of a spontaneous fracture due to such a metastasis led the surgeon to conclude that the fracture could not have been due to metastasis, simply because union did

occur Erdheim reports a detailed histologic study of the changes seen in a case of osteoclastic metastasis and presents an interpretation of the alterations noted. The patient was a woman, aged 74, who died of malignant bilateral papillary adenocystoma of the ovary, with multiple metastases in the heart, lungs, pancreas, sternum and vertebrae. Localization of the metastasis in the bone marrow led to disappearance of the marrow cells and to condensation of the reticulum of the marrow. The condensed reticulum became the stroma of the metastasis. Growth of the tumor led to widespread destruction and resorption of the spongy bone, destruction of bone was often associated with microfracture of the osseous trabeculae. Proliferation and fibrosis of the stroma of the tumor was followed by fatty change and necrosis of the tumor cells, apparently as the result of loss of blood supply. Disappearance of the tumor cells led to the formation of fibrous scar tissue, in which fat or marrow cells might later be deposited. The transformation of the scar tissue into fatty or cellular marrow appeared to be associated with a loss of the immunity that the tissue had developed during the process of disappearance of the tumor cells, since such secondarily formed marrow again became the site of metastasis. Although the metastases were of the osteoclastic type, some new formation of bone did actually occur about the periphery of the metastases. The new bone was formed both by osteoblastic apposition on the surface of old trabeculae and by direct calcification of fibrous and osteoid tissue.

O T SCHULTZ

BRONCHIAL CARCINOMA IN LEIPZIG, 1924-1929 M SCHLESINGER, *Ztschr f Krebsforsch* **31** 517, 1930

While the detailed figures given for the incidence of primary bronchial cancer in Leipzig for the six years under consideration are probably of little significance, since similar figures for Dusseldorf fail to show any indications of parallelism, the average occurrence in that time amounted to 13.54 per cent of all cancers found at autopsies, the highest ratio shown by any German city. The etiologic significance of this increased incidence remains as obscure as ever. Schlesinger is inclined to absolve automobile exhaust gases, as Dusseldorf, with relatively more cars per inhabitant, shows an appreciably lower rate, 11.42 per cent. Industrial gases can be dismissed for the same reason. Schlesinger doubts that the statistics definitely point to the operation of any irritant factor as the cause of the increase. The maximal incidence with regard to age was found in the sixth decade. Men were attacked more frequently than women, and showed a predominance of incidence on the right side, which was lacking in the other sex. The article includes a discussion of pathology, symptomatology and differential diagnosis of bronchial cancer.

H E EGGERS

CHIMNEY-SWEEPS' CANCER VANISHING L E RICHTER, *Ztschr f Krebsforsch* **31** 565, 1930

Richter states that chimney-sweeps' cancer, reported as occurring in Germany with some frequency in times past, is now almost nonexistent there. He ascribes its genesis to a combination of chemical thermal and mechanical irritation, and believes that greater precautionary cleanliness is the cause of its decrease. In England it still persists to a limited extent, and as it has always been more frequent there, Richter believes that English coal has greater cancerigenic power.

H E EGGERS

TESTICULAR CANCER WITH OLD EPIDIDYMAL TUBERCULOSIS F KIACES, *Ztschr f Krebsforsch* **31** 587, 1930

There is here reported a case of testicular cancer occurring four years after the appearance of epididymal tuberculosis. There was no evidence of the infection in the removed testis and the writer, dismissing the possibility of concurrent disease, believes that the cancer was due to the chronic irritation of the infection.

H E EGGERS

DIAGNOSTIC REACTIONS FOR CANCER R MAISLICH, *Ztschr f Krebsforsch* **31** , 605, 1930

A critical study of the various general reactions proposed for the diagnosis of cancer by laboratory methods leads Maislich to the conclusion that as yet no specific diagnostic measure has been developed, even though a few would seem to have limited clinical applicability

H E EGGERS

FAMILIAL TENDENCY TO OCCURRENCE OF SARCOMAS AND SPONTANEOUS FRACTURES R WERNER, *Ztschr f Krebsforsch* **32** 40, 1930

There is here reported the history of a family in which three children of parents apparently free from significant disease all showed marked tendency to fractures from ordinarily inadequate trauma. One of these died in childhood, but each of the survivors developed sarcoma at the site of the latest fracture during the third decade. A son of one of them showed the same liability to fracture and likewise died of sarcoma at the site of the latest fracture

H E EGGERS

THE SIGNIFICANCE OF SINGLE TRAUMA IN THE INCIDENCE OF CANCER M SCHAD, *Ztschr f Krebsforsch* **32** 43, 1930

From a study of previously reported cases, to which are appended two more by the writer, the following conclusions are reached. There are well authenticated instances of carcinoma originating locally after a single trauma, after a short period of latency and in the absence of other locally predisposing causes. Such cases are especially frequent in young persons, although with these there frequently is a longer period of latency than with older persons. There is a frequent direct relation of location and time to the injury, in which healing may or may not have occurred. No definite limit of time can be placed on the period of latency, it may be very short, or the cancerous development may occur after years of precancerous change. Not the degree of injury, but the extent and character of the reaction to it are the important factors in this connection. In any single case, the exact importance of the injury may be exceedingly difficult to determine

H E EGGERS

SPECIFIC MORPHOLOGIC CRITERIA OF TUMOR CELLS H HIRSCHFELD and E KJEL-RAWIDOWICZ, *Ztschr f Krebsforsch* **32** 139, 1930

These writers confirm the observations of Lipschutz as to the morphologic changes which the latter terms the "plastin reaction," in tumor cells. Like Lipschutz, they find these changes only in a limited portion of the cells, and they were not able to discover them more frequently in cultured tumor cells. They venture no opinion as to their value as fundamental criteria of malignancy

H E EGGERS

Medicolegal Pathology

THE RÔLE OF SYPHILIS IN THE ETIOLOGY OF ANGINA PECTORIS, CORONARY ARTERIOSCLEROSIS AND THROMBOSIS, AND OF SUDDEN CARDIAC DEATH ALDRED SCOTT WARTHIN, *Am Heart J* **6** 163, 1930

Active syphilitic lesions of the larger coronary branches are infrequent. They rarely produce occlusion of the vessel or lead to thrombosis or myocardial infarction. Arteriosclerosis of the coronaries, coronary occlusion, coronary thrombosis, myocardial infarction and angina pectoris are more frequent in latent syphilitic cases than in nonsyphilitic cases. Syphilis predisposes secondarily to coronary and aortic sclerosis and their resultant cardiac pathologic changes. Sudden death from heart failure was found almost five times as frequently in autopsies, in

syphilitic cases as in those in nonsyphilitic cases. In the majority of cases death was due to cardiac insufficiency and dilatation, resulting from a diffuse interstitial myocarditis of slight degree, leading eventually to fibrosis.

AUTHOR'S SUMMARY

CINCHOPHEN (ATOPHAN) POISONING. LAWRENCE PARSONS AND WARREN G. HARDING, JR., *Am J M Sc* **181** 115, 1931

Fifteen cases of fatal poisoning due to cinchophen have been recorded, including the four here reported. Striking pathologic changes in the liver have been found in all of the fatal cases studied at necropsy. In these cases, the total amount of the drug taken has varied from 37.5 to 7,050 Gm. Intensive dosage with cinchophen may produce acute hepatic degeneration. Long continued administration of the drug in moderate doses may result in subacute and chronic hepatic degeneration.

AUTHORS' SUMMARY

TRAUMATIC PNEUMOCEPHALUS. S. W. MILLER, R. N. KLEMMER and P. O. SNOKE, *J A M A* **96** 172, 1931

An interesting case, apparently the eleventh recorded, of air in the cerebral ventricles due to extensive cranial fractures is reported.

ELECTRIC SHOCK. W. MACLACHLAN, *J Indust Hyg* **12** 291, 1930

This report is based on a study of 479 selected cases of electric shock. Two types of cases are considered. 1. Those in which the patient receives an electric shock followed by unconsciousness in which the patient stops breathing, resuscitation is instituted, and in a variable length of time the patient breathes and lives. There were 323 such cases in this series. 2. Those in which an electric shock is followed by unconsciousness during which the patient stops breathing, resuscitation is started, but the patient fails to breathe and dies (156 cases). Complicated cases, such as extensive burns, a broken neck or back, etc., were rejected. It was thought that by limiting the investigation to these two definite types the comparison might disclose some definite trend of interest. In grouping cases by months, it was found that more deaths occurred in September, the maximum of successful resuscitation occurring in March. Less clothing is worn in summer and, together with perspiration, might account for more deaths in summer, there being less resistance at the point of contact. In grouping cases by the hour of the day, it was found that for some unaccountable reason the most successful resuscitations occurred between 1 and 2 p. m. In comparison by potentials of the circuit, the percentage of recoveries rises as the potential increases, probably because inexperienced workers handle lower potentials with less precaution and protection. High potentials are more protected and are handled by workmen of experience, usually with a poor or accidental contact and at times through an arc. It was found that the shorter the duration of the contact, the more was the success realized in resuscitation. The shorter the time between the shock and the institution of artificial respiration, the greater was the number of recoveries. The path of the current was found to have little or no effect.

C. G. WARNER

MIGRATORY BULLETS. LECIERCQ and MÜLLER, *Ann de med leg* **10** 33, 1930

Two cases are presented in which the bullet causing the death of the person had been found at autopsy to have been carried by the blood stream far from the end of its trajectory. In each case, the bullet entered the aorta and was found lodged in the left femoral artery.

A study of ten cadavers was made to determine why the bullet had followed the left instead of the right common iliac artery. The angle with the vertical made by the left common iliac artery was found to be 30 degrees, whereas that made by the right common iliac artery was 45 degrees. In nine cases the spur in the lumen of the aorta caused by the iliac bifurcation was not vertical, but inclined to the right.

The literature is reviewed, and migratory projectiles are divided into three groups, depending on whether the bullet penetrated to the veins, the cavities of the heart or the arteries. The majority of cases belong to the last group.

The medicolegal importance of a thorough search for such migratory bullets is emphasized.

EVAN BARTON

SUDDEN DEATH FROM HYPERTROPHY OF LINGUAL TONSIL MAHLE and SOUTTER, *Ann de med leg* 10 573, 1930

The case is reported of a man, aged 25, with chronic alcoholism, who was known to have died suddenly and quietly in his sleep. He had suffered from attacks of dyspnea and choking associated with retrosternal and epigastric pain for years, one such attack shortly preceding death.

At necropsy, in addition to marked hypertrophy of the lingual tonsil and hypertrophy of the palatine tonsils and of the lymphatic tissue adjacent to the epiglottis and the larynx, there were islands of hyperplastic lymphatic tissue in the omentum and mesentery. Multiple hemorrhages were visible microscopically in the adenoid tissue of the pharynx. There was no lymphatic hyperplasia in the spleen, thymus or follicles of the large intestine. A plug of mucus obstructed the larynx. The other organs were normal.

Death appeared to be due to asphyxia brought on by the lesions in the throat (a) mechanically from obstruction (b) reflexly, by laryngeal irritation, (c) by cardiorespiratory failure due to possible excessive swallowing of air associated with the condition of the throat, or (d) in association with one of the lymphatic diatheses in which sudden cardiac deaths are frequent.

EVAN BARTON

DEATH FROM PLEURAL INHIBITION C. RICHET, JR., and J. DUBLINEAU, *Ann de med leg* 10 773, 1930

Under varying circumstances, intercostal incisions were made into the pleura of rabbits. In an unanesthetized animal, the normal reflex is inhibition of the respiratory center, the severity of which, judged by the speed with which the animal dies, is directly proportional to the extent of the incision. If the field is anesthetized with procaine hydrochloride, death follows after twice as long a period.

These inhibitory reflexes are augmented by general anesthesia, traumatic shock and tracheal irritation. In the latter two conditions, the result is twofold: (1) a sudden inspiratory apnea from pleural shock, followed by (2) progressive inhibition of respiration until death occurs. The latter stage is due to associated inhibitory effects, which include (1) lowering of arterial tension (inhibition of the vasomotor center), (2) patellar, corneal and pupillary areflexia (inhibition of medullary centers) and (3) persistence of bright red blood in the carotid artery (inhibition of cellular activity).

Brief protocols are given of four experiments in which death followed suddenly after the rabbit's pleura or lung had been touched or pinched.

EVAN BARTON

RAPID DEATH FROM OSTEOOMA OF THE DURA MATER M. COIFFE and R. FAUQUEZ, *Ann de med leg* 11 48, 1931

A metal worker was found unconscious. During a short conscious interval, he complained of severe headache and stated that he had had a similar attack one year before. Death occurred the next day, and autopsy showed slight super-

ficial abrasions of the head and right knee, probably caused by a fall, passive hyperemia of both lungs and two osteophytes in the front of the falx cerebri, with slight compression of the right frontal lobe. The origin of the osteophytes is discussed. The sudden death is ascribed to vagus inhibition.

ARTHUR B. BRIANT

Technical

A QUICK METHOD FOR PREPARING HOMOGENEOUS SUSPENSIONS OF HEMOLYTIC STREPTOCOCCI. SOPHIE SPICER, *J. Immunol.* **19** 445, 1930

The strain to be used as antigen is grown on 0.2 per cent phosphate broth for three or four generations, and is transplanted twice a day. (Since the streptococci grow poorly on phosphate broth alone, better growth is obtained by heavier inoculation. A pipet should be used instead of a loop, using about 0.2 of 1 cc of the culture in about 5 cc of broth.) The day of the test, the antigen is planted in potato-phosphate broth. Approximately 40 cc of 0.2 per cent phosphate broth is poured into 100 cc bottles containing sterile potato strips. (This method requires the preparation of at least twice as many bottles as is usual.) The broth is then heavily seeded, 2 cc of culture being used for each bottle. The bottles are incubated at 37 C for not longer than two hours. They are shaken every fifteen minutes to stimulate growth. The two hour growth, however, is too thin to be used directly in the test. A proper emulsion is obtained as follows. The culture is centrifugated for thirty minutes at high speed to throw down the cells. The supernatant fluid is then poured off, and the cells are resuspended in enough of the same "supernatant" to give it a greater cloudiness than is desired, this is again centrifugated for five minutes at low speed to throw down any coarse granules that may be present. An antigen of desired cloudiness is thus obtained. This simple, quick and effective method of preparing the antigen gives hope of extensive diagnostic application of the agglutination test to the hemolytic streptococcus.

AUTHOR'S SUMMARY

ROENTGENOLOGIC STUDIES OF THE SPLEEN IN EXPERIMENTAL TUBERCULOSIS OF GUINEA-PIGS. S. LORAND, *Ztschr. f. Tuberk.* **56** 347, 1930

An operative method is described, by which small copper tags are clamped on the splenic capsule in animals. Roentgenologic observation shows then the alterations in the volume of the spleen that occur after infection with tubercle bacilli.

MAX PINNER

COMPLEMENT-FIXATION ACCORDING TO NEUBERG-KLOPSTOCK. R. LEVY, *Ztschr. f. Tuberk.* **57** 163, 1930

On the basis of examination in 340 cases the following conclusions regarding complement-fixation according to Neuberg-Klopstock are reached. A strongly positive reaction occurs only in cases in which there are active tuberculous lesions, and in from 13 to 17 per cent of these cases the reaction is weakly positive. The percentage of positive reactions in cases of active tuberculosis is altogether only 60 per cent. The procedure is too complicated to be of value in routine examinations, especially since its reliability is not great.

MAX PINNER

THE DIFFERENTIAL WHITE BLOOD CELL COUNT IN COLLAPSE THERAPY IN PULMONARY TUBERCULOSIS. R. GRIESBACH, *Ztschr. f. Tuberk.* **57** 177, 1930

The author based his serial studies of the white blood cell picture in patients with pulmonary tuberculosis on the assumption that in tuberculosis Schilling's

three phases of reaction have the same significance as in other infectious diseases. According to this concept, the hematologic reaction of the body against an infection is characterized by (1) a neutrophil phase of fight (Kampfphase), (2) a monocytic phase of defense (Abwehrphase) and (3) a lymphocytic phase of healing (Heilphase). Following numerous serial examinations of a large number of patients the author concludes that the differential white blood cell count is an indispensable means for prognostication and for the determination of the optimal collapse and of the proper time for reexpansion. It is particularly emphasized that only serial examinations have prognostic significance.

MAX PINNER

TUBERCLE BACILLI IN LARYNGEAL SMEARS G. VON HAIFNER, *Ztschr f Tuberk* 58 244, 1930

In smears from the larynx tubercle bacilli could be demonstrated in only a few cases in which they could not be found in the sputum. On the other hand, in many cases this method yielded negative results when the sputum was positive.

MAX PINNER

KAHN'S RAPID REACTION H. BOAS, *Acta path et microbiol Scand* (supp 3), p 69, 1930

In 5,361 cases the Kahn reaction of blood serum corresponded with the Wassermann reaction in 93 per cent. A nonspecific reaction occurred only once in 2,226 serums. The Kahn test is simpler and more sensitive than the Wassermann test.

Society Transactions

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, Jan 12, 1931

JOSEPH A CAPPS, *President, in the Chair*

THE RELATION OF SPLENECTOMY TO THE RESISTANCE OF RATS TO *TRYPANOSOMA LEWISI* W H TALIAFERRO, P R CANNON and S GOODLOE

Early investigators, especially Laveran and Mesnil (1901), reported that in an infection with *Trypanosoma lewisi* dividing forms occur in the blood of a rat only during the first few days, and that nonreproducing adults are found exclusively thereafter. Taliaferro (1924 and 1925) found that this peculiar life cycle is due to the resistance developed by the rat, since he demonstrated in the rat an antibody or reaction product which has the specific property of inhibiting the reproduction of the trypanosomes, but not of killing them. Regendanz and Kikuth (1927) concluded that the spleen, owing to its richness in cells of the reticulo-endothelial system, is one of the chief sites of the formation of this antibody, because after splenectomy the trypanosomes reproduce for from two to five days longer than normally. Marmorston-Gottesman and Perla (1930), Marmorston-Gottesman, Perla and Vorzimer (1930) and Perla and Marmorston-Gottesman (1930) essentially corroborated the results of Regendanz and Kikuth. Other investigators, notably Coventry (1930), demonstrated that there also develops in the rat a trypanocidal antibody, or possibly a series of them, which eventually sweep the trypanosomes from the blood and thereby terminate the infection.

The present investigation was undertaken to study the cellular basis of the resistance which rats develop against *T. lewisi* and in particular to ascertain what effect is produced by splenectomy on both the reproduction-inhibiting antibody and the lysin, when performed at different stages throughout an infection with *T. lewisi* and when performed on infected rats of different ages and in varying conditions of health. The effects were studied by ascertaining whether in a given infection the reproduction of the trypanosomes, as indicated by the presence of dividing, short or variable forms, occurred for more than the ordinary length of time or recurred after it had subsided, and whether the trypanosomes persisted in the rat's blood for a longer time than normally.

The results may be summarized briefly as follows. Splenectomy when performed on young healthy *Bartonella*-free rats from seven days prior to infection to forty-one days after infection does not markedly influence the formation of the reproduction-inhibiting antibody against *T. lewisi* (thirty-five rats). It does, however, markedly affect this antibody when performed on young rats infected with *Bartonella*¹ at similar intervals (thirty-three rats). In general the effect of splenectomy is slight when performed six days prior to infection, is more marked when performed on the same day as infection, is pronounced when performed from five to ten days after infection and is very slight or nil when performed from twenty-one to fifty-eight days after infection. For example, in normal infections the trypanosomes show reproduction for from five to nine days with a slight variation of from one to two days more, after which only adult forms of extremely uniform length occur, whereas in rats splenectomized on the fifth day after infection the trypanosomes exhibit reproduction (although to a lessened degree during this prolonged period) for from thirteen to thirty-one days, with a slight variation of from ten to ninety-days more, after which the infection assumes

1 This infection is found to occur in a latent form in practically all stock rats. Since it sometimes flares up after splenectomy, with fatal results, its occurrence in the present series of experiments had to be rigidly controlled.

its ordinary aspect with only adult forms occurring. Splenectomy in young rats suffering from a paratyphoid infection (four rats), gestation (four rats) or a blockade with india ink (eight rats) or in old rats infected with *Bartonella* (twenty rats) was marked by somewhat similar results. These data demonstrate that the spleen is of great importance in the formation of the reproduction-inhibiting antibody in infections with *T. lewisi*, and that the macrophage system has a functional level which develops so effectively in rats infected with *T. lewisi* that reproduction of the trypanosomes is checked by about the eighth day. This functional level is lowered by splenectomy and by other factors such as infection with *Bartonella*, pregnancy, etc., but no one of these seems sufficient to cause any marked disturbance of the infection with *T. lewisi*, whereas two or more by their additive effect markedly change the course of the infection.

Furthermore, splenectomy influences the trypanocidal antibody which is associated with the termination of the infection, since the infection lasts longer in splenectomized (seventy rats) than in unsplenectomized (thirty-two rats) animals. This effect is more marked when there is a concomitant infection with *Bartonella*.

The effect of splenectomy is specific, since castration, performed with about the same operative trauma as splenectomy, is without demonstrable effect on infection with *T. lewisi* (twenty rats).

During the course of this investigation certain secondary facts were demonstrated. Infection with *T. lewisi* in *Bartonella*-free rats (twenty-five rats) produces a significant increase in the size of the spleen during the first few days of infection and a demonstrable increase in histologic cellular activity as compared with that of normal healthy rats (twenty-six rats). Splenomegaly is more pronounced in rats infected with *Bartonella* alone (ninety-three rats) than in rats infected with *T. lewisi* alone (twenty-five rats) and is more pronounced in rats with both infections together (forty-eight rats) than in rats with either alone. *T. lewisi* is nonpathogenic, since death of the rats can be correlated with a concomitant *Bartonella* or paratyphoid infection.

DISCUSSION

PAUL CANNON. E. R. Long believes that certain intracellular conditions are unfavorable for the growth of *B. tuberculosis*. Against trypanosomes there may be similar intracellular inhibiting substances which are difficult to demonstrate.

I. PILOT. Have there been relapses following splenectomy in the latent period? Relapses following splenectomy have been noted in patients with malaria.

W. H. TALIAFERRO. Approximately one third of the rats have relapses following splenectomy.

THE COPPER AND IRON CONTENT OF THE BLOOD SERUM IN CANCER AND IN PREGNANCY. ARTHUR LOCKE and E. R. MAIN

The iron content of the hemoglobin-free serum of normal persons varies from a mean value of 1 microgram per cubic centimeter for young men to the value of 0.86 microgram per cubic centimeter for young women. It is slightly higher in old age and in pregnancy, is markedly higher in bilirubinemia and in the blood of the umbilical cord of new-born infants and may be slightly lower in advanced carcinoma and in leukemia. The copper content of the blood serum varies from a mean value of 0.80 microgram for young men to a value of 0.90 microgram for young women. It is slightly lower in bilirubinemia, is markedly lower in the blood of the umbilical cord of new-born infants, is slightly higher in leukemia, and is markedly higher in late pregnancy and in advanced carcinoma. The Cu:Fe ratio varies from the normal mean of 0.8—1.1 to the low values of 0.33—0.6:1 found in the blood of the umbilical cord of infants and in bilirubinemia to the high values of 1.8—2.3:1 found in pregnancy and in carcinoma. The lowered copper level in the fetal blood is paralleled by increased concentrations of the metal in the fetal tissues. The increased copper level in the blood of the pregnant mother is paralleled by an increased antitryptic index. The antitryptic index of the blood serum is also increased in carcinoma. Since the inactivating action on trypsin of the two sub-

stances, cyanide and cysteine, appears to be directed toward the cations of copper and iron contained in the catalytic nucleus of that enzyme, it is assumed that the action of antitrypsin may be similarly directed and that the affinity of antitrypsin for copper, thus expressed, may be the source of the rise in the concentration of copper in the blood serum which follows induction of a high antitryptic index. Further conclusions are drawn as to the relation of the increased level of copper and antitrypsin in the blood to certain of the sequelae of cancer and of pregnancy.

DISCUSSION

W F PETERSON Is there any relation between antitryptic activity and the unsaturated fatty acids?

A P LOCKE The content of unsaturated fatty acids fluctuates parallel with the antitryptic concentration.

COLONIES OF HEMOLYTIC STREPTOCOCCI ON CHOCOLATE AGAR RUTH TUNNICLIFF

While studying colonies of hemolytic streptococci on chocolate agar, I observed that those from typical cases of erysipelas and septic sore throat turn this medium green, generally at a temperature below 34 C, while those from scarlet fever produce no change, or occasionally a slight greening after several days' growth. On this medium, typical colonies of streptococci from scarlet fever are seen by a culture microscope, to form slightly granular, conical colonies, those from erysipelas smooth and convex colonies, while those from septic sore throat form colonies that are rough, indented, conical or convex and of the color of gun metal. Although the surface of the colony from septic sore throat is rough, the edge is regular.

Chocolate agar is prepared by adding 8 cc of defibrinated sheep blood to 150 cc of melted plain agar, heating the mixture to 90 C, cooling to 50 C and pouring into plates. Dextrose and lack of air appear to inhibit greening. According to McLeod and Gordon greening and bleaching of heated blood agar are due to the production of hydrogen peroxide. Dr Clarence Saelhof is studying this reaction and finds that pure hemoglobin, prepared from sheep blood according to the Marshall-Welker method, gives the same color change as whole blood. He can substitute gelatin for agar and still get greening. So far, attempts at growing streptococci in liquid mediums containing heated hemoglobin have not resulted in producing any distinctive changes in the spectroscopic bands.

Many cultures of hemolytic streptococci remain stable for years both culturally and serologically, but a few appear to dissociate, and the cocci from these dissociated colonies differ from the usual type, in colony formation and immunity reaction and sometimes in production of color on chocolate agar and in virulence.

Sixteen strains of hemolytic streptococci from erysipelas have been studied, which form the same type of colony and by the opsonic test belong to one group. They form large, smooth flat or slightly convex hemolytic colonies on blood agar and smooth, convex colonies on chocolate agar which is turned green. Five other streptococcus cultures from erysipelas have been examined, which appear to have dissociated from typical cultures and which form on blood agar four types of colonies atypical of erysipelas streptococci: pigmented yellowish, hemolytic, small hemolytic, green, and anhemolytic. All of these colonies, except the small hemolytic ones, produce green on chocolate agar. None of the atypical strains opsonify like streptococci from erysipelas.

Thirty strains of hemolytic streptococci from scarlet fever have been examined. They form small hemolytic colonies on blood agar and slightly granular conical colonies on chocolate agar, which is not changed in color. Here again many strains remain stable immunologically and culturally. One strain isolated in 1922 has shown no signs of changing until now. By aging on blood agar slants at the temperature of the incubator large moist spreading hemolytic colonies, which produce greening of chocolate agar, have been isolated from two old strains. These colonies on blood agar are similar to those from septic sore throat and the coccus

shows a capsular substance, but differs from the streptococcus from septic sore throat in that it does not form rough colonies with regular edges on chocolate agar. From a third strain of scarlet fever streptococci a small, smooth, convex colony and a flat, rough colony with irregular outline have been dissociated. The cocci from these atypical colonies no longer opsonify like the scarlet fever streptococcus group.

Aging also appears to change the streptococcus from septic sore throat, the typical rough colony with regular edges on chocolate agar dissociating into smooth, flat colonies, smooth, convex colonies and flat, rough colonies with irregular margins.

The two flat, rough colonies with irregular edges dissociated from strains of streptococci from scarlet fever and septic sore throat are typical of rough colonies dissociated from other bacterial cultures. They grow in clumps in dextrose broth, form long tangled chains, vary in size and shape and show bacillary and filamentous forms. The coccus from the original colonies grew diffusely in dextrose broth and formed short chains of round cocci. Cocci from the flat, rough colonies are avirulent for mice in contrast with those from the original colonies, which killed mice in twenty-four hours.

By subculturing in dextrose broth, by passage through animals and by aging, many of the dissociated streptococcus colonies may be caused to revert to the original type of colony, formation of color on chocolate agar and also the original immunologic group.

The difference in the color reaction and the colony formation on chocolate agar appears to be further evidence of a biologic difference between the streptococci from scarlet fever and those from erysipelas and corresponds to the specificity of the immunity tests and the bacteriophagic action.

The observation that dissociated colonies may appear in cultures of streptococci from scarlet fever and erysipelas, and that they no longer act immunologically like the specific group, may account for some of the confusing results in immunologic experiments with these streptococci.

DISCUSSION

I. PILOT. I have made similar studies of these streptococci and have obtained identical results.

D. J. DAVIS. These studies are interesting because they show that the hemolytic streptococci, as a group, can be integrated into specific strains. Have you studied hemolytic streptococci from various sources? There seems to be an overlapping among the streptococci, both clinically and bacteriologically.

RUTH TUNNICLIFF. I have tested many streptococci from various sources with immune serum and have not found organisms forming green colonies on chocolate agar to be opsonified by immune serum prepared against scarlet fever streptococci.

CHRONIC BRONCHITIS WITH FOREIGN BODY (ELASTIC FIBERS) REACTIONS IN THE LUNGS. FRANKLIN S. DuBOIS

The complete report will be published in the ARCHIVES OF PATHOLOGY.

AN UNUSUAL ODONTOMA. EDWARD H. HATTON

The odontoma is the rarest of tumors that arise from the odontogenic tissues. It takes its origin from a misplaced germ of a tooth and as a rule becomes clinically apparent during the course of the second dentition, that is, between the ages of 7 and 26. Because of its genesis it has a degree of relationship to adamantinoma, multilocular cyst, follicular cyst and dentigerous cyst.

The specimen to be described was removed by Dr. H. A. Potts from the mandible of a 3 year old boy because of the destruction of bone connected with it and because of the possibility of its being a malignant growth. It was 21 by 29 cm. in its two chief diameters and consisted of two portions, one somewhat

centrally located, but confined largely to one pole, and made up of rather densely calcified tissue, and a second part seemingly of soft tissues and occupying all of the opposite pole. Blocks were removed from both portions for histologic examination, decalcified, sectioned and stained by hematoxylin and eosin, thionine and picric acid and van Gieson's stain.

The densely calcified portion consisted of confused masses of dentine and enamel, in places separated by thin strands of connective tissue and remnants of enamel organ, as well as of a rudimentary dental pulp tissue. This portion was similar to the descriptions of the structure of composite odontomas.

The softer portion was essentially embryonic connective tissue through which extended numerous bands of enamel organ epithelium, very much like the anlage at a very early stage of the germs of the teeth. In this portion were the beginnings of rudimentary, badly formed teeth, not more than from 1 to 3 per section, in many instances, the arrangement was rather typical, in others, there was marked malformation.

The occurrence of an odontoma during the period of the first dentition is uncommon. The more densely calcified portion is older, probably than the softer portion. The structure of the latter part suggests a close relationship of this tumor to adamantinoma and the multilocular cyst.

NEW YORK PATHOLOGICAL SOCIETY

Anniversary Meeting, Jan 22, 1931

LEILA CHARLTON KNOX, *President, in the Chair*

LYMPHOSARCOMA OF THE ILEOCECAL JUNCTION, WITH DEMONSTRATION OF SPECIMENS JOSEPH S GREWAL and WARD J MACNEAL

L. R., a white man, aged 64, complained of a dull pain in the lower quadrant of the abdomen, on the right side, that had continued for one month, with occasional distention, followed by passage of much gas through the rectum. He had lost 15 pounds (6.8 Kg) in six months. The movements of the bowels had been irregular for one year. A tender, somewhat movable mass was palpable in the lower part of the abdomen, on the right side. The white cell count was 11,400, with 91 per cent polymorphonuclears. Urinalysis revealed a slight amount of albumin, together with hyaline and granular casts.

Resection of the lower ileum, cecum, ascending colon and a portion of the transverse colon was done by John F Erdmann. The specimen presents a portion of the ileum, the appendix, the cecum and a portion of the colon, 340 mm in length. The ulcerated tumor-bearing portion is 90 mm in length. The infiltration extends to about 50 mm beyond the ulceration along the wall of the ileum. The ileum is dilated above the tumor mass, which extends to the ileocecal junction. The entire thickness of the tumor is about 45 mm. The tumor mass consists of pale, homogeneous, translucent, firm tissue, extending along the wall of the ileum, where the mucosa is still intact. In the surrounding fat small, round, opaque, grayish spots resembling lymph nodes are present.

Microscopic Examination—The tumor mass consists mostly of lymphoid cells lying in the meshes of a rather scanty fibrillar supporting tissue. These cells vary considerably in size and shape, most of them contain rather abundant cytoplasm and large compact or vesicular, hyperchromatic nuclei. Occasional giant cells with multiple nuclei are also present. A few small mature lymphocytes are scattered throughout the tissue. Numerous figures of mitotic division are seen. A large number of eosinophils and large collections of polymorphonuclear cells are present subjacent to the ulcerated areas and outside the wall of the intestine in the adipose tissue.

MALIGNANT NEPHROSCLEROSIS, WITH DEMONSTRATION OF SPECIMENS JOSEPH S GREWAL and WARD J MACNEAL

N E, a white youth, aged 17, was well until six months before examination, then he had a cold and prolonged bronchitis with loss of appetite. For four months before examination he suffered from malaise, nausea, vomiting and diarrhea. The ankles became swollen three months before examination and the eyelids puffy two weeks before.

In the hospital he received a diet low in protein and salt-free. He received one transfusion of blood (500 cc). He gradually declined, with increasing anasarca and accumulation of nonprotein nitrogenous bodies in the blood. The red cell count was 3,000,000. Urinalysis showed a specific gravity of 1.012, abundant albumin, hyaline and granular casts and numerous pus cells.

At autopsy, each kidney weighed 280 Gm and presented the gross and microscopic picture of malignant nephrosclerosis in the uncontracted stage.

E K, a white man, aged 27, was ill in bed for several months seven years before examination, with kidney trouble. After an interval of good health the present illness began, four months before examination, with loss of appetite, malaise, headache, weakness and later dyspnea, blurred vision, diarrhea and edema of the legs. On admission to the hospital the patient was semicomatose and dyspneic. Examination of the blood showed 3,250,000 red cells, and 12,200 white cells, 90 per cent of which were polymorphonuclears, uric acid was 51, urea 144, creatinine 14.8, carbon dioxide combining power 26.8.

At autopsy the right kidney weighed 65 Gm and the left kidney 200 Gm, presenting the gross and the microscopic picture of malignant nephrosclerosis in the contracted and the uncontracted stages.

BACTERIAL ENDOCARDITIS IN HEART WITH INCOMPLETE INTERVENTRICULAR SEPTUM, WITH DEMONSTRATION OF SPECIMENS JOSEPH S GREWAL and WARD J MACNEAL

R W, a white man, a physician, aged 34, had had a plastic operation on the nose and upper lip in June, 1930, on return to duty he remained weak and tired quickly, later he lost his appetite and became nauseated, with distress after eating. On Aug 11, 1930, there was a sudden sharp pain in the back over the base of the right lung, aggravated by each respiration. Expectoration of blood and blood-tinged mucus began and continued, although the pleuritic pain gradually subsided. In the hospital his temperature ranged from 99.4 to 102 F, and to 103 F toward the end. From time to time there were renewed attacks of sharp pleuritic pain in different areas, with intervals of improvement. Meningitis closed the clinical history.

The past history included a record of eighteen surgical operations, most of them for double hare lip and cleft palate, but there was also an appendectomy.

At autopsy the heart weighed 575 Gm. There were active, soft red vegetations on the three aortic cusps, in which large colonies of streptococci were present. Incomplete ventricular septum with constriction of the right ventricle in the zone of the defect, marked hypertrophy of both ventricles and persistent foramen ovale were present. There were septic infarcts of lungs and kidney and terminal meningitis. Cultures yielded *Streptococcus viridans*.

DISCUSSION

WARD J MACNEAL. The peculiar interest of this last case is due in large measure to the fact that the patient was carefully observed during his life, particularly by himself. He contributed a great many of the records to his own chart, and these were made in an unusually objective manner for a patient. He seemed to take an exceptionally objective interest in his own illness and was willing to offer bets on the condition of his heart after the termination of his illness. One point that is mentioned is that his heart was not dilated. His heart held up to the end. What killed him was the meningitis. The heart, in spite of the congenital defects, was functioning reasonably well. During his college days

he was a mountain climber and an athlete, and with this defect in his heart he was able to hold his own with his fellows. Another interesting question has to do with the course of the blood through the heart. I am inclined to think that a good deal of the blood coming from the right auricle actually passed through the foramen ovale into the left auricle, and this because of the curious constriction which impeded the passage of blood from the right auricle through the right ventricle into the pulmonary arch. I think a considerable amount of the blood also passed through the opening in the ventricular septum, this opening led immediately to the region of this constriction in the right ventricle, and from there was forced through the pulmonary arch. The fact that the heart was able to do so well and was still in systole at autopsy, and that a meningeal infection terminated the patient's life, indicates what a congenitally defective heart may do.

RELATION OF MUCOUS GLANDS TO TONSIL LOUISE H. MEEKER

The mucous glands related to the tonsils are subject to wide variation both in location and in manner of opening to the surface. The usual location of these glands is in the connective tissue at the periphery of the tonsillar mass with ducts



Fig 1—Example of mucous gland ducts opening into crypts. The patient, aged 41, had had a previous tonsillectomy.

opening into adjacent crypts. A central location of mucous glands has been denied by many authors. My own observations have shown that there are many mucous glands located beneath the central portions of the tonsil.

The facts brought out by the studies of Fox, Grunwald, Goerke, Kingsbury and Levin, added to the controversial evidence of previous workers, Hammar,



Fig. 2—Example of minor branchiogenic cleft opening into the crypt above at the left. The patient, aged 40, had a history of repeated peritonsillar abscesses.

Levinstein and Maximow, force me to one conclusion. The tonsillar area in its development is the most unstable portion of the second pharyngeal pouch. The distribution of mucous glands related to the tonsils is an illustration of this instability. The varying type of epithelium found where mucous glands open into the crypts is a further illustration of the instability. Ducts lined by squamous

epithelium may open into the squamous epithelium of the crypts. The ducts may be single or in groups. Ducts may also be lined by cuboidal or columnar epithelium and the epithelium may be ciliated.

Ciliated epithelium found in the fundi of centrally located crypts is accepted by Dietrich for the first few years of life, and he considers it a fetal remnant. He mentions that he has seen it once in the tonsil of an adult. I have found it many times in the tonsillar crypts of adults and consider it a fetal remnant, because other fetal anomalies are occasionally associated with it.

It may be said in general that ciliated epithelium in the fundus of a crypt indicates the opening of the duct of a mucous gland nearby. The area lined by ciliated columnar epithelium is rarely more than 1 or 2 mm in diameter. Such ciliated epithelium occurs without relation to mucous glands, and then it is undoubtedly a persistent fetal remnant.

Hundreds of tonsils cut in both longitudinal and transverse planes have been examined. Many serial sections have been made. The observations in longitudinal sections agree with those of most observers. Transverse sections have yielded the most information about the unusual locations and manner of opening on the surface. In addition to the variations already noted I have found occasional glands from 10 to 15 mm in diameter and a few glands wholly or in part duplicating the parotid gland in structure.

The anatomic differences noted assist one in understanding the pathology of the tonsil. This is especially true in the case of the so-called recurrent tonsil of the adult and in that of peritonsillar abscess.

I have found true lymphoid tissue extending along mucous glands deep into the pharyngeal fascia and muscle and not along blood vessels. Grunwald gets very close to this description, and Hett and Butterfield found extensions of lymph follicles about mucous glands in the gorilla and Vervet monkey. This extra-tonsillar lymphoid tissue may proliferate extensively after excision of the tonsil proper. Peritonsillar abscesses may arise in this periglandular lymphoid tissue.

DISCUSSION

WARD I. MACNEAL. I think that probably abundance of material and lack of adequate study are nowhere so marked as in connection with the particular group of pathologic conditions represented by tonsillar material. I had the opportunity to sit with some prominent laryngologists of this city who were discussing diseases of the tonsil. In a naive fashion I asked one of them how he recognized a pathologic tonsil. He thought a minute and then said, "If I can discover the tonsil in the throat of a patient, it is a diseased tonsil." This is a challenge to the pathologists to ascertain the nature of this particular tissue and to state their observations in such a way as to make an impression on those who deal with this region of the body clinically. I believe that the facts presented here will appeal to our clinical friends, at least, I hope they will, because they serve to explain one of the difficulties with which the laryngologist occasionally meets, namely, that of the so-called bad result of tonsillectomy. I hope that this paper will engage their attention and help them to see that there may be something worth while in a study of the structure of the tonsils.

SEROLOGIC REACTIONS IN A CASE OF TUBERCULOSIS OF THE SEROUS MEMBRANS

ADELAIDE B. BAYLIS

A physician, aged 43, exhibited symptoms that made it difficult to form a diagnosis. Laboratory tests for *Bacillus typhosus*, *B. paratyphosus A* and *B* and *Brucella abortus* gave negative results, also the result of a complement-fixation test for tuberculosis was negative. The only positive information was that afforded by the Vernes flocculation test for tuberculosis, which gave a reaction indicative of active tuberculosis. This was disregarded because unsupported by the complement-fixation test and roentgenologic films. Necropsy revealed milary

tuberculosis of the serous membranes. It is suggested that the complement-fixation test might be more successful if the antigen employed were made from organisms isolated from particular anatomic regions of the body, also that the Vernes test is a valuable adjunct in cases in which diagnosis is difficult.

DISCUSSION

BLAKE F. DONALDSON (by invitation). It was my good fortune to see this patient clinically. We were very much puzzled by this positive reaction for tuberculosis. The patient had been febrile for a long time, and it seemed incredible to us that we could establish the diagnosis of tuberculosis on this test alone when in the x-ray picture the lungs looked almost entirely clear five or six days before the patient died. I think that it is important that we should have a large number of these tests in similar cases, so that we may determine how reliable they are.

WARD J. MACNEAL. I should like to sound a word of caution which was sounded here last year, and that is that the Vernes test may give a highly positive flocculation when the patient has not tuberculosis. This is particularly true when the result of the test goes above 100. It has happened that when we got flocculations of from 120 to 150, we dealt with generalized malignant neoplasms. It is obvious that there are involved here factors that are not clearly understood. The test has a place and is useful, and I believe the word of warning should be coupled with the papers which come out from this laboratory, so that it will not be for some one else to offer this criticism. I am glad to offer it, and I know that Miss Baylis is glad to have it offered.

ADELAIDE B. BAYLIS. I should like to add that that word of warning also comes from Vernes' laboratory. In his recent work on tuberculosis, he said that in diseases in which there is destruction of tissue one must be careful in interpreting high readings of Vernes' flocculation test.

INFLUENCE OF PUS AND BLOOD ON THE ACTION OF BACTERIOPHAGE. MARTHA APPLEBAUM and WARD J. MACNEAL.

Purulent exudate from human lesions, as well as sterile purulent exudate from the rabbit, exerts a marked inhibitory influence on the lytic action of the staphylococcus bacteriophage. This behavior in vitro offers an explanation for the persistent survival of the bacteria in purulent collections within the body of a patient receiving treatment with potent bacteriophage. Even when diluted 1:1,000, a purulent exudate may show some inhibitory effect in vitro. Heating the pus at 60 C. for thirty minutes diminishes this inhibitory power only to a slight degree.

Undiluted citrated blood, defibrinated blood and diluted blood serum exercise a similar inhibitory influence on the staphylococcus bacteriophage, but there is considerable variation in the behavior of different bacterial strains and possibly also in the behavior of different races of bacteriophage.

The analogous experiments with the colon bacillus and its bacteriophage were negative in their results under the experimental conditions employed.

The paper is to appear in full in the *Journal of Infectious Diseases*.

DISCUSSION

WARD J. MACNEAL. Some extremely modest friend has asked me in regard to a particular body fluid, namely the urine. We have presented a paper concerning the behavior of these agents in urine, and the influence of the hydrogen ion concentration of urine, and we have in progress other experiments that include the combined influence of pus and blood. Here there are so many variables that very complete records are required.

EFFECT OF VARIATIONS IN THE WEATHER ON THE SYMPTOMS OF PATIENTS WITH HAY-FEVER. MARJORIE R. HOPKINS.

A study of these conditions was made at the New York Post-Graduate Hospital in 1929 and 1930 in connection with the clinic for patients with hay-fever. The

daily symptoms of patients with hay-fever caused by ragweed who had received treatment with extract of ragweed pollen for ten weeks previous to the onset of their symptoms, as well as from August 15 to September 29, were recorded and correlated with the daily temperature, the humidity, the pollen count and the rainfall as noted in Central Park, New York

It was found that precipitation, a low temperature and a high humidity caused a lessening of the ragweed pollen content of the air and thus lessened the symptoms of the patients

Days of no precipitation, high temperature and low humidity increased the dissemination of the pollen, and thus increased the severity of the symptoms in the patients

DISCUSSION

W C SPAIN (by invitation) I think that Miss Hopkins has shown us very clearly the relationship between the symptoms of the patient and the production of pollen. Of course we have known of it for a long time from the clinical point of view, but I do not believe that it has before been shown in such a graphic way as Miss Hopkins has presented it here tonight

WARD J MACNEAL There has been some newspaper publicity lately in regard to something suspended in the atmosphere over Europe, which has been reported to have given rise to a considerable amount of disease, and I think that possibly some of our friends in this country have thought that the explanation of this was due to suspended particles in the air to which the population of certain districts had become sensitive. This is just a theoretical explanation which is always possible when we have very little exact knowledge

Book Reviews

DIE GASBEHANDLUNG BOSARTIGER GESCHWULSTE By BERNHARD FISCHER-WASLLS, o o Professor der allgemeinen Pathologie und pathologischen Anatomie an der Universität, Direktor des Senckenbergischen Pathologischen Instituts zu Frankfurt am Main, unter Mitwirkung von Priv.-Doz Dr W Bungeler, Dr J Heeren, Dr S Heinsheimer, Dr G Joos Price, 65 marks Pp 472, with 82 illustrations, some colored, and numerous tables Munich J F Bergmann, 1930

This account of the gas therapy for malignant tumors during the three years from 1927 to 1929 at the Senckenberg Pathological Institute of the University of Frankfurt appeared as volume 39 of the *Frankfurter Zeitschrift für Pathologie*

The treatment rests on Warburg's discovery that cancer cells elaborate a large amount of lactic acid Attempts were made to alter this fermentative metabolism by causing mice with tumors to inhale oxygen, but it proved so unsatisfactory that other means of stimulating cell respiration were soon added The most promising among these adjuvants was carbon dioxide, which was employed for the double purpose of increasing tissue respiration and mitigating the untoward effects of pure oxygen In order to enhance its activity, however, the oxygen-carbon dioxide mixture was combined with other measures, such as dextrose, insulin, acids, metals, dyes, the roentgen rays and so on the best of which turned out to be acids given intravenously

Methods thought to be effective in the mouse were later tried out on inoperable tumors in man, thus two patients suffering from inoperable cancer of the digestive tract were given oxygen and carbon dioxide with hydrochloric acid by mouth, since the introduction of an acid into the circulation was considered too hazardous In both cases the tumor seemed to disappear, but Fischer-Wasels, well aware of the dangers of premature optimism, concludes only that the treatment deserves full investigation

The material described occupies the first three articles in the book The remaining seven include such problems as the blood and tissues in acidosis and alkalosis, the oxygen taken up by the body during the inhalation of different gas mixtures, predisposition to tumors, lactic acid in the blood and tissues and the effect of various substances on the metabolism of organs in vitro

On the chemistry involved in the work under consideration, the reviewer is not competent to pass judgment, nor can the ultimate value of this work to the patient be forecast from the outcome in two cases It should be pointed out, however, that the fermentative type of respiration occurs not only in the cancer cell but in certain normal cells, as even Warburg himself now acknowledges, and that the degree to which it may be present in cancer often bears not the slightest relation to the malignancy of the neoplasm It may be, therefore, that treatment with gas for tumors rests on an insecure foundation In any case, the few charts introduced to demonstrate its efficacy against tumors in mice are inadequate to prove anything, particularly as some of the disappearing tumors had ulcerated, for this and other reasons the investigation as a whole has been bitterly attacked by Caspari in recent numbers of the *Zeitschrift für Krebsforschung*

THE PATHOLOGY OF INTERNAL DISEASES By WILLIAM BOYD, M.D., M.R.C.P. (Ed.), Dipl. Psych., F.R.S.C., Professor of Pathology in the University of Manitoba, Pathologist to the Winnipeg General Hospital, Winnipeg, Canada Cloth, \$10 net Pp 888, with 298 illustrations Philadelphia Lea & Febiger, 1931

The title of this book raises the question, What does the author mean by "the pathology of internal diseases?" The word pathology is used in the large sense to include not only structural changes, the pathologic anatomy of disease, but pathogen-

esis and physiologic physiology as well. The contents consequently correspond roughly to the sections in textbooks and systems of internal medicine that deal with pathologic anatomy and pathogenesis, with special emphasis on the relation of the clinical manifestations to the associated lesions. By internal disease the author refers to the diseases usually found in the medical wards of a teaching hospital or, put in another way, to the diseases that would be covered by a higher examination in internal medicine. The so-called infectious fevers, a term of rather ill defined significance, and "conditions which have no anatomical basis" have been left out of consideration. The diseases caused by animal parasites have also been omitted—trichinosis is not mentioned. No satisfactory reason is apparent for this limitation in scope. The book is intended to be a companion volume to "Surgical Pathology" by the same author, and there is considerable overlapping. A strict division into surgical and medical pathology cannot be carried out satisfactorily. One wishes that the author, who is a skilled and successful writer, might have written one comprehensive work on pathology in relation to internal medicine and surgery.

The following synopsis of the contents will show the scope of the volume under consideration: diseases of the heart, arteries, respiratory system (larynx, bronchi, lungs and pleura), stomach and duodenum, intestines, liver and gallbladder, pancreas, kidneys, suprarenal glands, thyroid gland, parathyroid glands, pituitary body, the blood, bone marrow, spleen, lymph nodes, thymus gland and nervous system. There is a useful list of references at the end of each chapter. The chapters on the suprarenal, the thyroid, the parathyroid and the pituitary glands contain much of interest. The statement on page 541 concerning the lack of physiologic action of extracts of the pituitary needs revision. The introduction to the chapter on Bright's disease is well written. The illustrations, which deal with gross and microscopic changes, are good. The style is clear and pleasant. Physicians will find this an interesting and valuable book.

GEWEBSPROLIFERATION UND SAUREBASENGLEICHGEWICHT By DR. RUDOLF BALINT, o. o. Universitäts-Professor, Direktor der I. Med. Klinik der Pazmany Peter-Universität in Budapest und DR. STEFAN WEISS, Assistent der I. Med. Klinik der Pazmany Peter-Universität in Budapest. Mit einem Vorwort von Baron A. v. Koranyi, o. o. Universitäts-Professor, Direktor der III. Med. Klinik der Pazmany Peter-Universität in Budapest. Price, 16.80 marks. Pp. 209, with 59 illustrations. Berlin: Julius Springer, 1930.

This monograph is a contribution to experimental pathology. It had its origin in the observations of Balint on the treatment for gastric ulcer with alkalis, which led him to the conclusion that the healing of the ulcers is induced more by systemic alkalization than by local alkalization of the ulcer. It was found that the reaction of the blood in patients with ulcer is more toward the acid than toward the normal side, even in healed stages or after operative removal of the ulcer. A gastric ulcer in a patient whose stomach was excluded from the digestive tract by anastomosis of an artificial esophagus with the intestine healed rapidly under the intravenous administration of alkali. These and other observations, together with the fact that the literature gives contradictory testimony on the effects of acids and alkalis on inflammation and repair, led to an extended series of experimental studies. A discussion of the literature is followed with reports of experiments on the effects of administration of alkalis and acids to animals with various lesions. The results go to show that acids interfere with proliferation of the tissue and that alkalis promote the growth of cells and reparative processes. Among the conditions in which these effects were observed were inflammations produced with turpentine, reactions of the skin of man to tuberculin, experimental gastric ulcers, wounds of the skin and muscles, cultures from tissues, the various phases of tuberculous reactions, the formation and repair of bone and the growth of carcinoma in mice. An extensive bibliography adds to the value of this interesting report on experimental studies that have much practical significance and which undoubtedly will serve as the starting point for further investigations.

PATHOLOGISCHE ANATOMIE UND HISTOLOGIE DER VERGIFTUNGEN Bearbeitet von DR ELSE PETRI, Berlin Volume 11 (Bildet Band X vom Handbuch der speziellen pathologischen Anatomie und Histologie herausgegeben von F Henke und O Lubarsch) Price, 144 marks Pp 724, with 96 illustrations, many in colors Berlin Julius Springer, 1930

This book contains a vast amount of reliable information, conveniently arranged, concerning the structural lesions in the various forms of poisoning In the first part of the book the material is grouped according to the actions of single poisons on individual organs The poisons are classed partly according to their chemical nature and partly according to their pharmacologic and biologic nature as follows metals, metalloids, acids and alkalis, nitrocompounds, narcotics, glucosids, alkaloids, animal and vegetable fats, oils, camphor, terpenes, balsams, resins, poisonous plants, poisonous animals and animal poisons, food poisonings, and hormones—insulin, extract of pituitary, thyroïdin and epinephrine

The second and smaller part of the book consists of differential diagnostic tables, showing the changes caused in the organs by different poisons These tables, the arrangement of which has involved a great deal of work, will be of help in reaching safe conclusions in difficult cases

There is a voluminous bibliography (seventy-four pages) divided according to main subjects, with references listed alphabetically according to the names of the authors Finally come an index of names and one of subjects The illustrations, all text figures, mostly in color, are of exceptional interest The book, which covers a large field thoroughly, has no rival It will be of use to all who are interested in the pathologic anatomy and histology of poisoning—pathologists, medicolegal examiners, industrial physicians, toxicologists, pharmacologists, physiologic chemists and workers in chemotherapy

PROBLEMS AND METHODS OF RESEARCH IN PROTOZOOLOGY By Twenty-Seven Contributors Edited by Robert Hegner, Professor of Protozoology, and Justin Andrews, Associate in Protozoology, in the Johns Hopkins University School of Hygiene and Public Health Cloth Price, \$5 Pp 532, with 32 illustrations New York The Macmillan Company, 1930

This book is devoted to an orienting presentation by American protozoologists of the problems and methods of research in protozoology It is intended to help students and beginning, as well as older, investigators in this now active field of work There are forty-two chapters by twenty-seven contributors, each one of whom has written on some phase or phases of protozoology with which he is especially familiar Parasitic protozoa receive the primary consideration Kofoid, Craig, Rees and Haughwout have written chapters on amebiasis, and Hegner, Barber and Komp, Manwell, and Taliaferro on malaria There is a helpful bibliography of the books, journals and original literature concerning protozoa The book illustrates the rapid progress of the knowledge of the protozoa, especially the parasitic, and their relations It will be of great value to all who are interested actively in protozoology Physicians and pathologists will find it helpful in their consideration of the protozoan diseases of man

BRIGHT'S DISEASE OBSERVATIONS ON THE COURSES OF DIFFERENT TYPES AND ON THE RESULTANT CHANGES IN RENAL ANATOMY By D D VAN SLYKE, EDGAR STILLMAN, EGERT MOLLER, W EHRLICH, J F MCINTOSH, L LEITER, E M MACKAY, R R HANNON, N S MOORE and CHRISTOPHER JOHNSTON From the Hospital of the Rockefeller Institute for Medical Research Medicine Monographs XVIII Price, \$3 Pp 236, with 66 charts and 41 figures, 4 in color Baltimore Williams & Wilkins Company, 1930

This monograph contains detailed reports of observations, continued for from a few weeks to several years, on sixty-seven patients with Bright's disease, hemorrhagic, sclerotic and degenerative The morphologic changes in seventeen of the

cases are described and illustrated. The views of Volhard and Fahr and of Addison that the three types of Bright's disease differ in nature are supported. It is emphasized that a gradual decrease in the ability to secrete urea frequently develops in the degenerative form, or nephrosis. The view that the kind of change in the kidneys can be determined by observations during life is supported. The clinical, chemical and functional observations are presented for each patient in charted form. The variations in the results of the observations on the three types of Bright's disease are striking, and the case records will be studied in detail by those interested in Bright's disease. The book presents the results of a model nosographic study by modern methods. It will be valued by pathologists who wish to correlate the anatomic changes in the kidney with the types of Bright's disease.

THE PATHOLOGY OF DIABETES* MELLITUS. By SHIELDS WARREN. Cloth. Price, \$3.75. Pp. 212, with 83 engravings and 2 colored plates. Philadelphia: Lea & Febiger, 1930.

This book is far more inclusive than might be expected in one of about 200 pages. There is a directness of approach that immediately leads to the heart of things. Theories are cited and historical features introduced, when appropriate, and the facts are presented in logical order. Throughout the work methods are outlined promoting intimacy and confidence in the results of the investigation. An especially noteworthy feature is the use of biopsy material from numerous sources. A correlation is thus established between the manifestations of disease in a patient, his biopsy specimens and the observations at postmortem examinations on the bodies of other diabetic patients. The 83 engravings and 2 colored plates, most of which are excellent, enhance the value of the text. A bibliography for each chapter provides ready references. In places the work is necessarily sketchy owing to a general dearth of information.

Books Received

THE PATHOLOGY OF GENERALIZED VACCINIA IN RABBITS National Institute of Health Bulletin no 156 Ralph D Lillie, Passed Assistant Surgeon, and Charles Armstrong, Surgeon, U S Public Health Service Price, 70 cents Pp 95, with 57 black and white and 8 colored plates Washington, D C Government Printing Office, 1930

TEXT-BOOK OF GYNECOLOGY By Arthur H Curtis, M D, Professor and Head of the Department of Obstetrics and Gynecology, Northwestern University Medical School, Chief of the Gynecological Service, Passavant Memorial Hospital, Chicago Price, cloth, \$5 Pp 380, with 222 original illustrations Philadelphia W B Saunders Company, 1930

RECENT ADVANCES IN THE STUDY OF RHEUMATISM By Frederic John Poynton, M D, F R C P (Lond), Physician, University College Hospital, Senior Physician, Hospital for Sick Children, Great Ormond Street, and Bernard Schlesinger, M A, M D (Camb), M R C P (Lond), Physician to the Children's Department, Royal Northern Hospital, Physician to Outpatients, Hospital for Sick Children Price, \$3 50 Pp 313, with 25 illustrations Philadelphia P Blakiston's Son & Company, 1931

DIE BIOLOGIE DER PERSON EIN HANDBUCH DER ALLGEMEINEN UND SPEZIELLEN KONSTITUTIONSLEHRE UNTER MITARBEIT ZAHLREICHER FACHMANNER Von Prof Dr T Brugsch und Prof Dr F H Lewy Band 2 Liefening 17 Price, 35 marks Berlin Urban & Schwarzenberg, 1931

AN INTRODUCTION TO PRACTICAL BACTERIOLOGY A GUIDE TO BACTERIOLOGICAL LABORATORY WORK By T J Mackie, M D, D P H Professor of Bacteriology, University of Edinburgh, and J E McCartney, M D, D Sc Edition 3 Price, \$3 50 Pp 421 New York William Wood & Company, 1931

A TEXT-BOOK OF MEDICAL JURISPRUDENCE AND TOXICOLOGY By John Glaister, M D (Glas), D P H (Camb), F R S E, Professor of Forensic Medicine, University of Glasgow, etc In collaboration with John Glaister, Jr, M B, Ch B (Glas), M D (Hons) (Glas), D Sc (Glas), Barrister-at-Law of the Inner Temple, London, Professor of Forensic Medicine, University of Egypt, Cairo, etc Edition 5 Price, \$8 50 Pp 954, with 139 illustrations New York William Wood & Company, 1931

EFFECTS OF A FAT-FREE DIET ON THE STRUCTURE OF THE KIDNEY IN RATS

V G BORLAND, M A

AND

C M JACKSON, M D

MINNEAPOLIS

Burr and Burr¹ produced a new deficiency disease in rats by the rigid exclusion of fat from the diet. Since bloody urine and an abnormal appearance of the kidneys were often observed, they concluded that renal disorder may be an important factor in this disease. The primary object in the present study was to determine the nature and extent of the structural changes found in the kidneys of these rats. Dr. George O. Burr allowed us to investigate this material.

MATERIAL AND METHODS

Table 1 gives the composition of the basal diets used in most cases, including casein (highly purified), sucrose and salt mixture, supplemented in some cases by lard or other fats. The fats were carefully extracted from the yeast (used for vitamin B complex). The non-saponifiable matter of the cod liver oil ("fraction AD" for vitamins A and D) and of the wheat germ ("fraction E" for vitamin E) were used. The details concerning the diet are given in the publications by Burr and Burr¹.

Burr and Burr found that rats reared, after weaning (at 3 weeks of age), on this fat-free diet soon begin to show a characteristic disorder. The disease is characterized externally by an abnormal, scaly condition of the skin, especially on the dorsa of the feet. This condition usually becomes apparent between the fiftieth and ninetieth day of life. The tail becomes irregularly and coarsely scaled, the tip may become inflamed and swollen, and from 1 to 3 cm. of it may become necrotic and drop off. The hair on the back is often filled with dandruff. There is a tendency for the hair to fall out, especially around the face, neck and back. Growth is subnormal and usually ceases at about 5 months of

* Submitted for publication, Oct 4, 1930

From the Department of Anatomy, University of Minnesota. The work was aided by a grant from the Medical Research Fund of the University of Minnesota.

¹ Burr, G. O., and Burr, M. M. A New Deficiency Disease Produced by the Rigid Exclusion of Fat from the Diet. *J. Biol. Chem.* **82**: 345, 1929, On the Nature and Role of the Fatty Acids Essential in Nutrition, *ibid.* **86**: 587, 1930.

age After a stationary period of variable length the rat loses weight rapidly and dies Bloody urine is frequently noted in the later stages

The cutaneous lesions in this new disease suggest pellagra But 0.7 Gm of whole yeast powder given daily failed to protect the rats from the disorder, and an increased dosage of yeast failed to cure This would apparently exclude pellagra

To test the adequacy of the extract of cod liver oil as a source of vitamins A and D, three rats were reared on the fatless diet plus 10 drops of lard daily No extract of cod liver oil was given In the seventh week all had xerophthalmia, and one died, whereas their controls, receiving the usual dose of the extract of cod liver oil, were growing normally with no signs of deficiency at 10 months of age It was also found that doubling the dose of the extract of cod liver oil, or the addition of butter failed to cure sick animals on the fatless diet The disorder therefore cannot be ascribed to any deficiency in vitamins A

TABLE 1—*Composition of Basal Diets Used (Burr and Burr¹)*

Diet	Pure Casein, %	Sucrose, %	Salt Mixture, %	Lard, %
550	24.0	72.1	3.9	0
550A	16.0	80.1	3.9	0
550B	12.0	84.1	3.9	0
560	30.1	45.1	4.8	20
560A	20.0	55.1	4.8	20
560B	15.0	60.1	4.8	20

* Modifications and accessories used are explained in the text

and D The presence or absence of vitamin E in the diet likewise makes no difference in the appearance of the characteristic disorder

When an addition of 20 per cent of lard or even 10 drops of lard daily, was included in the diet of the young rats, comparatively good growth resulted, and no lesions of the skin and tail were present Animals receiving even as little fat as is present in 3 drops of cod liver oil daily (when this was given for vitamins A and D instead of the concentrate of cod liver oil) remained generally healthy for a period of a year, although some abnormal scales were found on the feet and tail

Once the disease has developed, rats can apparently be cured by the addition of 20 per cent of lard to the diet, or even by the addition of 10 drops of lard daily (2 per cent of diet) It was also found that the disease can be readily prevented or cured by the addition of 2 per cent of certain fatty acids to the diet, but the nonsaponifiable portion of fats and glycerol were ineffective for preventing or curing the disease Apparently some necessary fats (linoleic acid and perhaps others) cannot be synthesized in the organism and must be supplied in the diet

For the present study, the kidneys from 124 rats were available These included a series from the animals used by Burr and Burr,¹ together with those from a

number of other rats used in more recent experiments by Burr and Jackson. The rats were partly of the Wistar albino strain and partly of the Long-Evans pied strain. The results were the same in both cases. Both male and female rats were used, but no sex differences were apparent. All the animals were reared in the colony at the Institute of Anatomy, where excellent care and housing are provided.

The test rats were on the experiment for variable periods, the average age at autopsy being 278 days. Rats 20 and 21 (table 2) were exceptionally young (from 72 to 74 days), while rats 13 to 17 and 96 to 111 were unusually old (about 19 months). All the rats were killed with chloroform, those found dead being excluded from the present study. The 124 rats used have been classified in 10 groups, depending largely on the diets used and the microscopic changes in the kidneys, as shown in table 2. In general (unless otherwise specified), the rats were placed first on diet 550, and later changed to diets 550A and 550B, since lower levels of protein suffice with advancing age. The special diets of the various groups will be given in the section on observations.

At autopsy (by C. M. Jackson) the kidneys were usually placed in 4 per cent formaldehyde. As these experiments with fatless diets have been in progress for about two years, the fixation in some cases was necessarily prolonged. Group 2 (test rats) and rats 43 to 46 in group 4 (cured rats) were preserved in formaldehyde from fifteen to seventeen months. This is unfortunate, since prolonged fixation probably changes somewhat the finer histologic structure and staining capacity. In particular, it lessens the amount of demonstrable fat, as shown by Bell² and others. The kidneys from the eight stock animals were fixed in formaldehyde for only from twenty-four to forty-eight hours. Kidneys from the remaining groups were fixed from one to six months. Zenker fixation was also used in a few instances.

For general histologic study, sections a few millimeters thick were embedded in paraffin, cut in sections at 5 microns and stained with hematoxylin-eosin or Mallory's aniline blue. Several other stains were also used. For a study of fat (or lipid) content, frozen sections were made and stained with sudan III or scarlet red. Von Kossa's silver nitrate method was used for the demonstration of calcium deposits.

OBSERVATIONS

As mentioned, the 124 rats used in this study were classified into 10 groups, as shown in table 2. These include 3 groups of test rats, 2 groups of cured rats and 5 groups of control animals.

RATS USED FOR TESTS

Forty-two of the 124 rats were reared on the test (fatless) diets, and are classified in 3 groups: 1, 2 and 3.

Group 1—As shown in table 2, group 1 included twenty-one animals. They were reared at first on basal diet 550, later on 550A and 550B (table 1). These diets were supplemented daily with ether-extracted yeast and "fraction AD", and with the exception of rats 13 to 18, they also received the wheat germ ("fraction E").

² Bell, E. T. On the Occurrence of Fat in the Epithelium, Cartilage, and Muscle Fibers of the O. *Am. J. Anat.* 9:401, 1909.

TABLE 2—*Individual Data on the Kidneys in Rats Used in the Experiments and in Normal Rats*

Number	Classification	Uncalcified Degeneration	Fat Content	Casts in Medulla	Hyperplasia of Pelvic Epithelium	Infiltration by Round Cells
Group 1 Test Rats (Strictly Fatless Diet)						
1	p+++ c++	p+++ c++	p+, c+++	+f, a	++	++
2		p+	p+, c+			+
3	p-	p+, c+	p+, c+	+f	+++	+++
4	p-+++, c++	p+	p+++ c+	+++f, a	++	+
5		p+, c++	p+++ c++	+++f		+
6		p+	p+, c++	+++f		+++
7		p+	p+			+++
8	c++	p+++ c+	p+++ c+	+++f, a	++	
9	c+	p+++	p+, c+	+++f, a	+	+
10	c+	p+++	p+, c+	+++f, a	+	
11	c++	p+++	p+++ c+	+++f, a		
12	p-	p+++ c+	p+++ c+	+f		++
13	c-	p+++ c+	p+++ c+++	+++f, a		+
14	p+++ c+++	p+++	p+, c+	+++f, a	+++	+
15	p++ c++	p+++ c++	p+++ c+++	+++f, a	+	+
16	p+, c-	p+++	p+++ c++	+++f	+	+
17	c-	p+++	p+, c+	+++f, a		
18	c-		p+, c+	+f, a		
19	p++ c+	p+, c+	p+, c+		+	+
20						+
21	c±					+
Group 2 Test Rats (Fatless Diet Supplemented with Cod Liver Oil)						
22		p+				+
23		p+			+	
24					+	+
25						+
26		p+				+
27						+
28				+f, a		
29		p+++ c+	p±		+	++
30		c+	p±			++
31	c+	c+			+	++
32						
33	c+	p+++ c+	p+			+
Group 3 Test Rats (Fatless Diet Supplemented with Various Ineffective Fats)						
34	c++	p+				+
35	c+	p+	p+, c+			+
36	c++	p+, c++	p+++ c++	a		
37	c+	c+	p+, c++	f		+
38	c+++	p+, c+	p+, c+++	f		+
39	p++ c++	p+++ c+	p+++ c+++	f, a	+	+
40	c+++	p+, c±	p+++ c+++	f, a		+
41	c+++	c-				
42	c+					
Group 4 Cured Rats (Strictly Fatless Diet Later Cured by Adding 2 to 20 per Cent of Lard)						
43		p+				+
44		p+				+
45						+
46		p+, c±				+
47		c±	p-			+++
48			p+	c+	+++f, a	+
49	p±		p+, c+	+++f	+	+
50						
51						
Group 5 Cured Rats (Fatless Diet, Cured by Adding Fat in Various Forms)						
52	c+++	p+++ c-	p+, c+	+f		+
53	p+	p+++	p+, c+	+f, a	+	
54	p+, c-	c+	p+, c+	+f	++	+
55	c+++	p+++ c+	p+, c+			
56	c-	p+, c+	p+	+a		++
57	c+++	p+, c++	p+++ c-	+++f, +a		+
58	c+	c±	p+++ c+++	+++f		+
59	c+	p+ c+	p+, c+++	+++f		+
60		p+	p+, c+	+f		+
61			c±			+
62	c+++	p+, c+	c±			+
63	c+++	c-	p+, c+			+
64		p+	c+	+a		+

* Location of lesions designated by p papillary region (medulla), c, cortical tubules. Casts are designated as f (fatty), a (albuminous) or c (calcified). The sign ± indicates merely traces while - - - or +++ represent slight amount, moderate amount or abundance of the corresponding character.

TABLE 2—Individual Data on the Kidneys in Rats Used in the Experiments and in Normal Rats ²—Continued

Number	Calcification	Uncalcified Degeneration	Fat Content	Casts in Medulla	Hyperplasia of Pelvic Epithelium	Infiltration by Round Cells
Group 5 Continued						
65			p+, e+++	+f		+
66			p+, e++			+
67	p+, e±		p+, e++		+	+
68	p+, e+	p+, e±	p+	+++		
69	p+, e++	p+, e+	p+, e+	+e	+	—
70	e±	p+	p+, e+++	+++f		++
71	e+++		p++ e+			
72	p±, e+	p+			+	++
73	e+	p+	e+			+++
74	e++	e+	p+, e+			+
75	e++					—
76	e+++	e±	p+, e+	+f		+
77		p+	p+, e+			
78	e++	p+, e+	e+++			—
79	e+++		p+, e+	+++f		++(?)
80	e±	p±				+
81		e+	p++ e+			++
82	p+	p++	p+, e+		++	+++
83	e++		p+, e+	+++f, e		+++
84	e+	p+	p+, e+	+f		+
85	e++	p+, e+	p+, e+			
86	e++	p±, e+	p+			+
Group 6 Control Rats (Fattish Diet Plus 10 Drops of Lard Daily)						
87			p±			
88		p+	p+			—
89		p+	p+			
90			p±, e±			—
91						
92						
93			p+			+
94	e±		p+			+
95		e+				—
Group 7 Control Rats (20 per Cent of Lard in the Diet)						
96		e++	e+			
97		p+	p+, e+	+f		+
98		e++	p±, e+			+
99		e++	p±			+
100			p+, e±	+f, a		
101		p+, e+	p++ e+	+f, a		++
102		p+, e+	p++ e+			
Group 8 Control Rats (Fattish Diet Plus Various Kinds of Fat Daily)						
103		e++	p+, e+	+++f, a		+
104		p+, e+	p+			
105						+
106			p±, e±			+
107			e±			+
108		p+	p+, e+			+
109	e+	e+	p±, e±			
110	e+	p±	p+, e+	+f	+	+
111		p+	p±			+
Group 9 Normal Rats (Diet Containing Starch)						
112		p±	p±			+
113		p±	p±			+
114			p±			+
115			p±			+
116		p+	p+			+
Group 10 Normal Rats (Stock Diet)						
117			p±			+
118			p±			+
119			p±			+
120			p±			+
121						—
122			p±			+
123						+
124						+

With three exceptions, the rats of this group exhibited varying degrees of poor nutrition at autopsy. Emaciation was most marked in the oldest rats (13 to 17 inclusive). The tail was coarsely scaled in every case, and the coat of hair thin and rough. For the whole group, the body weight averaged 26.8 per cent below the Wistar norm³ (for corresponding body length), the range being from 7 to 41 per cent.

Grossly, the kidneys usually appeared large and pale. The surface varied somewhat, that of some of the organs being finely pitted, while that of others was coarsely granular and sometimes sprinkled with small, whitish specks. Very fine pitting apparently occurs sometimes in normal kidneys, a circumstance which may be a source of confusion. The kidneys of the rats in this group averaged 21.8 per cent above the Wistar norm for weight according to body length, ranging from 18 per cent below to 105 per cent above normal.

Microscopically, variations from the normal controls appeared in the cortex, the medulla and the pelvis. They will be described in this order. The distribution of the lesions is shown in table 2.

Cortex. In sections of the cortex, the lesions noted were restricted chiefly to the tubules, the glomeruli showing no definite changes. The most striking and characteristic lesion in this region was the appearance, in certain isolated tubules, of cells that stained a deep blue with hematoxylin and black with von Kossa's stain, indicating the deposition of calcium. Usually the lumen of each of these tubules contained a certain amount of debris, which was also calcified, so that in cross-section the usual appearance was that of a large calcareous cast surrounded by the basement membrane alone, the cells having partially disintegrated (fig. 1). In a few cases, the deposits appeared merely as fine cytoplasmic granules in the cells of the tubules. In such cases the nucleus sometimes appeared uncalcified. But when more dense calcification had taken place, the cells fused, and the nuclei were not visible.

These calcified tubules occurred singly and were usually found near the corticomedullary border, although they were not necessarily limited to this region. The process in general was degenerative (a "nephrosis"), since usually no appearance of associated inflammation was noted. There was some evidence that this calcification might have been preceded by fatty degeneration and desquamation of tubular epithelium. However, the tubular cells immediately adjacent to the calcified tubules and the cells throughout the remainder of the cortex, except in these few isolated tubules, were usually normal in appearance.

3 Donaldson H. H. *The Rat* (ed. 2), *Memoirs of the Wistar Institute of Anatomy*. Philadelphia, Wistar Institute, 1924.

Calcification of cortical tubules was demonstrated in fifteen of the twenty-one kidneys in this group (table 2). A typical section across the kidney presented from three to ten strongly calcified tubules arranged near the corticomedullary border. In a few cases, however, various stages of cellular degeneration appeared over the entire cortex, and in some of these calcification was more widespread.

Rats 20 and 21 were killed at the age of 74 and 72 days, respectively, having been on the fatless diet only about seven weeks. They demonstrated merely some of the earliest manifestations of the resulting disorder. The external appearance of both was normal, except for a slight abnormal scaliness of the dorsa of the feet and the tip of the tail.

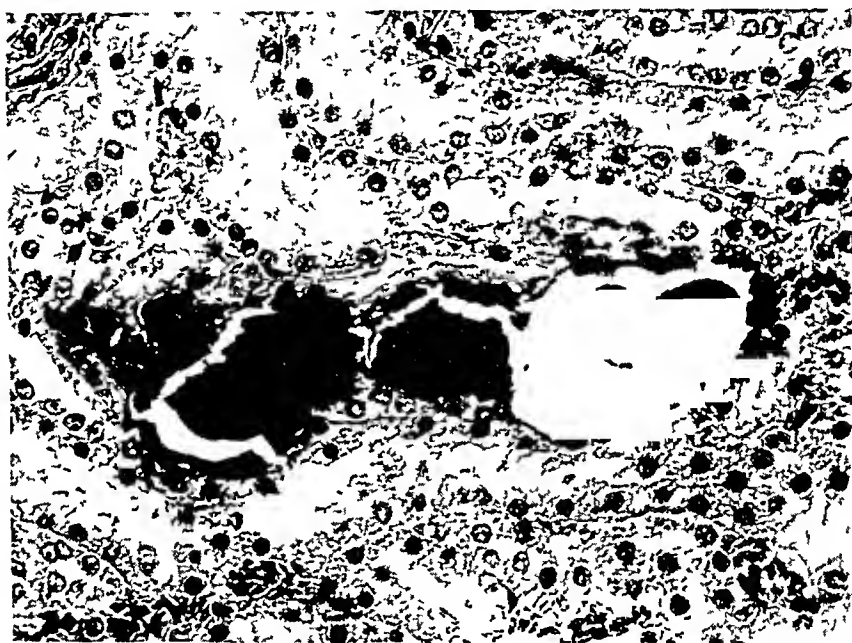


Fig 1—Photograph of a section of the kidney from test rat 11, showing calcification in a cortical tubule. Hematoxylin-eosin stain, $\times 330$.

Grossly, the kidneys were normal, except for enlargement. Microscopically, aside from a small amount of infiltration by round cells in both, the only lesion was a slight calcification in some of the cortical tubules in rat 21.

As mentioned, uncalcified degeneration also sometimes occurred in the cortical tubular epithelium. When present (fig 2), it appeared, as a rule, throughout the cortex. The cytoplasm in the degenerating epithelium stained less readily, became fragmented and sloughed off into the lumen of the tubule. The nuclei showed various stages of pyknosis and karyolysis. This type of widespread cellular degeneration was noted in eight of the twenty-one kidneys in this test group. It might have been related to the general condition of the animal, since many of these

rats were emaciated at autopsy. The picture closely resembles that shown by Jackson⁴ for typical renal degeneration during severe inanition.

In cases in which the cytoplasm of the degenerating cells was not entirely disintegrated, frozen sections stained with sudan III showed an apparent increase in intracellular fat (or lipid). This fat appeared as small and medium-sized droplets, either in the basal portion of the cell or throughout the cytoplasm. Both proximal and distal convoluted tubules and the ascending limb of Henle's loop occasionally showed this fatty change. In some cases, the fatty condition of the tubules was widespread throughout the entire cortex. At other times it was

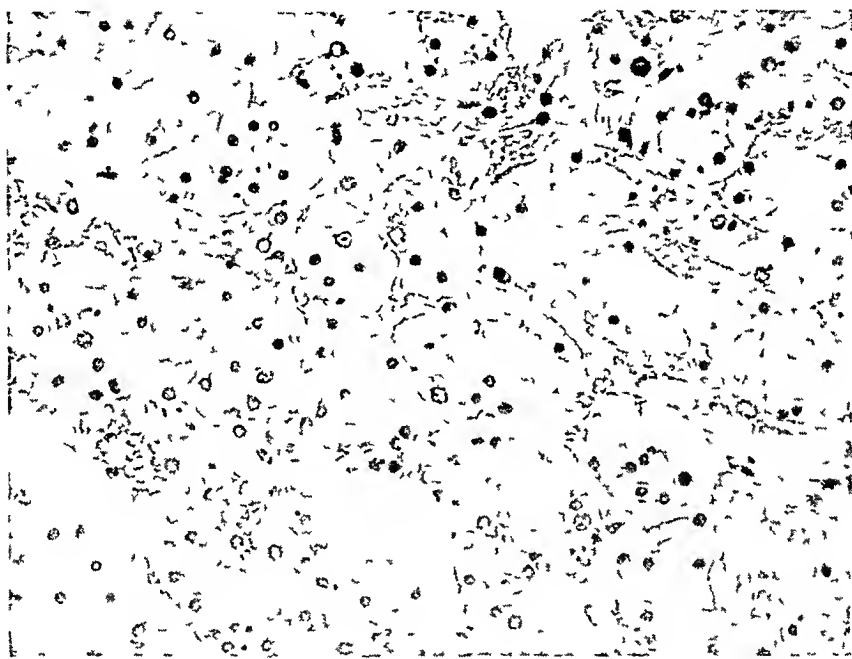


Fig 2—Photomicrograph of a section of the renal cortex from test rat 29, showing the typical uncalcified cortical tubular degeneration. Hematoxylin-eosin stain, $\times 300$.

apparent in isolated groups of tubules only, and then the individual cells usually showed only a moderate amount. From table 2 it can be seen that group 1 of the test rats nearly all showed more or less fat in the cells of the cortical tubules.

The occurrence of demonstrable fat where there was no obvious appearance of degeneration would seem to indicate that fat is normally present in the tubular epithelium. It may be possible, however, that the appearance of fat in the renal cells was merely the first indication of

⁴ Jackson, C. M. *The Effects of Inanition and Malnutrition on Growth and Structure*, Philadelphia, P. Blakiston's Son & Company, 1925.

degenerative change, since the kidneys of normal stock animals showed no fat in these cells. This question will be considered later under "Comment and Conclusions." Associated with this fatty metamorphosis of the cortical tubules were certain fatty casts in the medulla, which will be described later.

Focal points of round cell (lymphocytic) infiltration were observed in fourteen of the twenty-one kidneys of this group. The groups of round cells occurred around some of the small arteries and between the tubules. A typical section of the entire kidney showed from four to six such areas. This was probably indicative of some sort of a chronic inflammatory process, but since it was found also in the kidneys of normal stock animals, it was not characteristic of the fat-deficiency disease.

In a few cases, an inflammation of low grade apparently involved also the renal epithelium, small areas being present where the tubules were shrunken and their outlines obliterated, with an associated infiltration by round cells and an increase in connective tissue fibers. No definite changes were noted in the glomeruli. No polymorphonuclear leukocytes indicating acute inflammation were found. These shrunken areas, when near the renal surface, accounted for the gross appearance of a coarsely pitted surface, but the finely pitted or granular areas frequently noted at autopsy could not be correlated with any microscopic lesions.

In several cases, a dilation of some of the cortical tubules was noted. This appeared mainly in the larger collecting tubules, and was possibly due to some obstruction to the flow of urine in the papillary ducts. Somewhat similar, but more extensive, lesions representing spontaneous interstitial nephritis have frequently been observed in rats and other laboratory animals (Jackson⁵).

Medulla. In this group (on strictly fatless diet), the lesions shown in sections of the medulla were often restricted to the cells of the papillary ducts. In comparison with those of normal controls, the boundaries of the cells in the degenerative regions appeared indistinct, the cytoplasm atrophic and sometimes vacuolated, and the nuclei pale, with a deeply staining nuclear membrane.

Frozen sections stained with sudan III often showed in these degenerative areas many fine droplets of fat (or lipoid) in the epithelial cells of the medullary ducts and also in the adjacent interstitial tissue. In other cases, the lumina of the ducts were filled with many small fat droplets. These formed large, elongated cylindric casts (fig. 3). Often

⁵ Jackson, C. M. Spontaneous Nephritis and Compensatory Renal Hypertrophy in Albino Rats on Diet Deficient in Vitamin A, *Proc. Soc. Exper. Biol. & Med.* 22:410, 1925.

this fatty material in the lumen was intermingled with a homogeneous substance that stained pale blue with hematoxylin, and may have been precipitated albumin. These fatty casts appeared more numerous when the fatty change in the cortical tubules was most pronounced. They were possibly due in part to fat dioplets which had escaped into the lumina of the corresponding convoluted tubules and later had passed down into the ducts of the medulla, where they appeared as casts.

In the extreme cases (rats 1, 3, 4, 12, 14, 15 and 16), the renal papilla appeared largely necrotic and much of it might be sloughed off into the pelvis (fig 4). In these cases, irregular masses of the necrotic material stained a deep blue with hematoxylin and black with von



Fig 3—Photomicrograph of a longitudinal section of the renal medulla from test rat 4, showing fatty casts in the ducts. Sudan III stain, $\times 180$.

Kossa's stain, indicating that here in the medulla (as in the cortex) calcification had taken place. Higher up in the pyramid in such cases casts of fatty-albuminous material sometimes appeared in the lumina of the degenerating ducts, and, as the necrotic area was approached, this material, as well as the degenerating tissue, became intermingled with the deposits of calcium. The appearance of the calcification in a cross-section of the renal papilla is shown in figure 5.

This picture of necrosis and calcification in the papilla was present in eight of the twenty-one kidneys in this group. In two of the eight, bacteria and a few polymorphonuclear leukocytes were present in the necrotic area. These, however, apparently represented superimposed



Fig 4—Photomicrograph of a section of the kidney from test rat 3, showing necrosis, apical disintegration and calcification in the papilla, also hyperplasia of the pelvic epithelium. Hematoxylin-eosin stain, $\times 27$. The letters indicate, *d*, papillary duct, *c*, calcification, *epi*, proliferated pelvic epithelium, and *f*, perirenal fat.

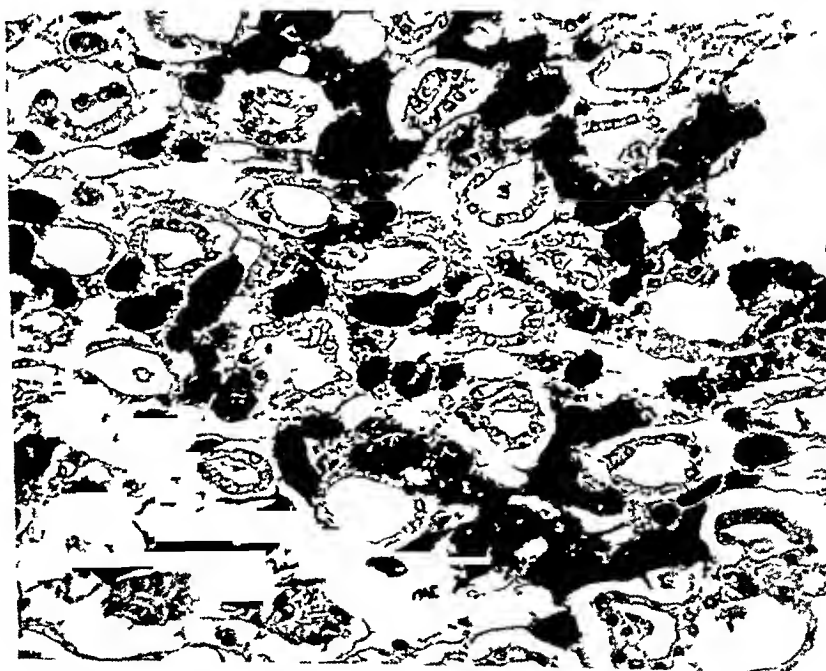


Fig 5—Photomicrograph of a cross-section of the renal papilla from test rat 16, showing areas of calcification (black). Hematoxylin-eosin stain, $\times 150$.

infections, since in the remaining kidneys no evidence of inflammatory reaction could be found

Renal Pelvis In ten of twenty-one kidneys of this group (on strictly fatless diets), a proliferation of the pelvic epithelium was noted. This epithelium, which is normally of a low transitional type, became hyperplastic and greatly thickened in certain regions. This sometimes gave the impression of a very small papilloma with a broad base (fig 4). No evidence of epithelial cornification was present. These hyperplastic areas were most marked where necrosis was present in the adjacent tip of the renal papilla.

In several cases in which the papilla was intact, the surface epithelium lining it, although not proliferated, showed some fine irregular droplets of fat in the cells. The hyperplastic pelvic epithelium contained no fatty material, however.

Group 2—As shown in table 2, this group included twelve test rats. Five of these (rats 23, 24, 26, 27 and 28) were kept throughout on the diet high in protein (24 per cent)—diet 550, the others were changed as usual from 550 to 550 A and 550 B. A daily supplement of "fraction AD" was given, but later a change was made to 2 drops of cod liver oil. The yeast and wheat germ supplements were also unmodified in some cases. This dietary experiment therefore constituted a modified test, since some fat was present in the cod liver oil, the ordinary yeast (which contains 1.5 per cent fat), and the wheat germ (which contains 10 per cent fat). Moreover, rat 18 had been partially cured by the addition of from 5 to 15 drops of coconut oil to the diet daily.

This group presented differences from group 1, the manifestations of the disease being, in general, much less pronounced. The average body weight was only 8.6 per cent below the Wistar norm, range, 9 per cent above to 26 per cent below. Poor general nutrition was noted in only one case. The remaining eleven were either normal or nearly so as regards the general condition of the body. More or less typical lesions of the tail, however, were present in every case, except one.

The kidneys of this group were large, but entirely normal in surface appearance. They averaged 25 per cent heavier than the Wistar norm, range, from 11 per cent below to 58 per cent above normal.

Microscopically, the kidneys of group 2 showed much less severe lesions than those of group 1, as shown clearly in table 2. Calcification of the cortical tubules was present in only two cases. Cortical tubular degeneration was present in four rats, but in no case was any fatty material found in the cortex. However, this lack of fat means little, since the kidneys of this group were fixed in formaldehyde for from fifteen to seventeen months.

Infiltration by round cells occurred with about the same frequency as in group 1. The small atrophic areas that were responsible for the coarse pits in the surfaces of the kidneys of group 1 were not present in group 2. This was in accordance with the normal appearance of the surface in the kidneys of this group.

In five of the twelve kidneys of group 2, a slight or moderate degeneration of the epithelial cells in the papillary ducts was noted. None of these showed necrosis or calcification. Fat (or lipid) was demonstrable in this region in only three cases, as a few scattered droplets in the cells of the papillary ducts and interstitial tissue. Here again, however, the lack of fat may have been due to long preservation in formaldehyde. In one case only, a few "albuminous" casts were present in some small ducts in the upper part of the pyramid.

A slight proliferation of pelvic epithelium was indicated in four cases of this group.

Group 3—As shown in table 2, this group included nine test rats. They were reared throughout on diet 550 B (low in protein), supplemented with "fraction AD," extracted yeast and wheat germ ("fraction E"). In this group, cures were attempted with various fats (hydrogenated coconut oil, liver lipoids, methyl oleate, butter fat), but these failed to restore normal body weight and general external appearance. Therefore the results in this group may be considered as those of a modified test.

In general condition the rats in this group closely resembled those of group 1. All exhibited poor nutrition at autopsy, and characteristic lesions of the skin were present in every case. Body weight in this group averaged 27 (range, from 15 to 31) per cent below the Wistar norm.

Microscopically (table 2, group 3), certain cortical tubules presented distinct and characteristic calcification in every case. Likewise, the other lesions, in general, agreed closely with those of group 1. Hyperplasia of the pelvic epithelium, however, occurred in only one case. Calcification was present in the papilla only once, and in that case little apical necrosis appeared.

CURED RATS

Forty-four rats were apparently cured of the disease (with regard to body weight and cutaneous lesions) by the addition of varying amounts and types of fat to the diet. These cured rats are divided into two groups, 4 and 5.

Group 4—As shown in table 2, group 4 included nine rats. Rats 47 to 51 were reared on diet 550 B, low in protein and fatless, rats 43 to 46, as usual, on diet 550, and later, on 550 A and 550 B. All these

diets were supplemented daily with extracted yeast, "fraction AD" and wheat germ ("fraction E") Rats 43 and 44 received daily the alcoholic extract of 1 Gm of fresh placenta Later a cure was obtained in rats 43 to 46 by changing them to diet 560 (containing 20 per cent of lard), and in rats 47 to 51 by the daily addition to their food of from 10 to 15 drops of lard (from 2 to 3 per cent of the diet)

As shown by the records, the cutaneous lesions in this group disappeared, and body weight (which had become nearly stationary) increased rapidly At autopsy, these rats were in excellent condition, with the exception of a slight abnormal scaliness of the tip of the tail in rat 46 Body weight was practically normal, averaging only 4 per cent below the Wistar norm for length

The kidneys of this group at autopsy appeared normal grossly, and in weight averaged 12 per cent above the Wistar norm, range, from 8 per cent below to 12 per cent above

Histologically, the kidneys of this group usually showed little difference from those of the normal controls In three cases, however, the cells of the papillary ducts showed slight degeneration In two cases, the cortical tubules also appeared somewhat degenerated However, none showed the more severe lesions, such as necrosis and calcification except very slight calcification in the papilla of rat 50 Infiltration by round cell was noted in six of the nine cases in this group The absence of demonstrable cortical fat in rats 43 to 46 may again have been due to preservation for about seventeen months in formaldehyde

Group 5—In general, the thirty-five rats in group 5 appeared normal as regards external condition But since the cures were all apparently ineffective, so far as the renal lesions were concerned, these rats were grouped separately The first six rats in this group were reared at first on fatless diet 550, later being transferred to diets 550 A and 550 B The others of this group were reared throughout on diet 550 B, low in protein All the diets were supplemented with "fraction AD," yeast and (usually) wheat germ ("fraction E") After the typical external symptoms had appeared, these rats were (apparently) cured by the addition of small amounts (usually 5 drops daily) of fat in various forms These included linseed oil, corn oil, olive oil, egg lecithin, methyl stearate, methyl linolate and poppy seed oil

Rats 82 to 86, inclusive, constituted a group of "late cures," since they were kept on the test diet for a relatively longer period than the other cured animals These late cures were achieved by the addition of 10 drops of corn oil to the diet daily

At autopsy, the general condition of group 5 was good or fair With the exception of a slight abnormal scaling of the tail in rats 67

82 and 85 and a slight roughening of the coat of hair in rats 54, 63 and 64, no lesions of the skin were present. The average body weight of this group was 10.2 per cent below the Wistar norm, range, 18 above to 29 per cent below.

However, these supposedly cured rats showed in histologic preparations rather striking lesions of the kidneys, as is evident in table 2. Calcification of the cortical tubules was present to a variable extent in twenty-six of the thirty-five rats in this group. Uncalcified degeneration in the cortical tubules was frequent, but not severe in any case. An increase in intracellular fat (or lipid) in these cells was nearly constant. Infiltration by round cells was present to about the same extent as previously described for other groups.

Degeneration of cells of the papillary ducts was present in twenty-one of the thirty-five cases, with calcification and necrosis in the papilla in seven of the twenty-one. The necrotic areas, however, were always relatively small, and never so extensive as those in group 1 (fig. 4). An increase of fat (or lipid) appeared in the cells and lumina of these ducts.

Hyperplasia of pelvic epithelium was present (usually slight) in six of the thirty-five cases.

CONTROL RATS

Thirty-eight rats were available in this study as controls for the experiments with fatless diets. Of these, three groups (6, 7 and 8) were reared on the test (basal fatless) diets with the addition of various kinds and amounts of fat as preventives. Additional controls were provided by five rats (group 9) on a normal diet containing starch (no 560 substituting starch for sucrose), and by eight rats (group 10) on the normal diet of the stock colony. Since groups 7 and 8 were obviously abnormal in general condition, the normal controls for this study included merely groups 6, 9 and 10.

Group 6—This normal control group consisted of nine rats. Of these, rats 87 to 90 were reared on diet 550, later on 550 A and 550 B. The remaining rats (91 to 95) were kept throughout on the diet low in protein, 550 B. All received the normal supplements of "fraction AD," yeast, wheat germ ("fraction E") and 10 drops of lard daily. Externally these rats appeared normal in every way. Body weight was nearly normal, averaging only 5.3 per cent below the Wistar norm. The range was from 6 per cent above to 13 per cent below normal.

The kidneys of this group appeared normal grossly. They averaged in weight 1.5 per cent above the Wistar norm ranging from 3 per cent below to 14 per cent above normal.

Microscopically, also, the kidneys of this group were nearly normal (table 2). The cortex was normal in all respects as compared with that of normal stock animals, with the exception of a very slight appearance of calcification in rat 94. Infiltration by round cells was present in five of the nine cases. In two cases a slight appearance of (uncalcified) degeneration was noted in the cells of the papillary ducts. In four cases an apparent increase in intracellular fat (or lipid) was noted, and in two other cases a few scattered fat droplets (probably normal) were present in the lower portion of the pyramid.

Group 7—The seven rats of group 7 were reared on diet 560 (20 per cent lard), supplemented by normal amounts of vitamins. It is worthy of note that the rats in groups 7 and 8 of the controls were approximately twice as old as most of the rats in the other groups.

In external appearance, the rats of this group, although not entirely normal, were not markedly abnormal. As a whole, nutrition was fair. The skin frequently appeared abnormal, although the lesions typical of the disorder caused by the fatless diet did not occur. Body weight averaged 14.4 per cent below the Wistar norm, ranging from 11 to 19 per cent below. The kidneys usually appeared grossly normal, in weight they averaged 4 per cent above the Wistar norm, ranging from 8 per cent below to 30 per cent above.

In sections of the cortex in this group (table 2) no calcification was found, but the renal tubules showed more or less degeneration in five of the seven cases, with an apparent increase in intracellular fat (or lipid). Infiltration by round cells was noted in three of the seven cases.

In this group and in group 8 of the controls (also in rat 79), a peculiar condition was noted that was not present in the other groups. Yellowish-brown inclusion bodies were found in many of the cells of the convoluted tubules. These bodies varied in size from about half to about twice the size of the nucleus, the larger size being more common. The larger bodies were circular in outline, whereas the smaller ones were more irregular. Sometimes several of the smaller bodies could be found in a single cell. When present, they were found widespread over the entire cortex. In five of the seven kidneys of group 7, these inclusion bodies were found and in four of these, cortical tubular degeneration was noted. The cells in which they were found, however, were not severely degenerated. They were also present in unstained sections. Since these groups of rats were much older than most of the others, it is possible that these inclusion bodies may have been related to the pigmentary degeneration occasionally described as occurring in aged individuals.

The cells of the papillary ducts appeared degenerated in three of the seven rats in group 7. An increase in fat (or lipid) content of these cells was noted in six cases. No necrosis or calcification was found in the papillary region. Fatty-albuminous casts appeared in the medullary ducts in three cases.

Group 8—Group 8 consisted of nine rats reared on diet 550 (changed later to 550 A and 550 B), with the usual supplements of yeast and "fraction AD," plus fat in various forms (mostly 10 drops of lard or of olive oil, or 1 Gm. of fresh liver daily). The last two rats (110 and 111) received a varied treatment, and are not strictly comparable with the others of this group.

The body weight of this group averaged 18.5 per cent below the Wistar norm, ranging from 3 per cent above to 35 per cent below. Nutrition was distinctly poor in rats 103 to 107 inclusive, but good in rats 108 and 109.

Histologically, in sections of the cortex in this group uncalcified degeneration of cortical tubular cells appeared in three of the nine cases and calcification in two cases. An apparent slight increase in intra-cellular fat (or lipid) in the cortical region was noted in three cases, with traces (normal?) in three others. The inclusion bodies described for group 7 were found in three cases. Slight infiltration by round cells was present, as found in groups previously described.

In the papillary region of the medulla, fatty (or lipidal) material was present in seven of the nine rats in this group, three presenting the normal traces only. Uncalcified degeneration of cells of the papillary ducts was noted in four cases. Necrosis and calcification of the papilla did not occur in any of this group. Two cases showed the fatty-albuminous casts in some of the smaller medullary ducts.

In one case a typical hyperplasia of the pelvic epithelium was present.

Group 9, on Diet Containing Starch—This group of five rats was reared on essentially the same type of normal diet as group 6, except that corn starch was substituted for sucrose.

Normal external appearance was noted in every rat of this group. The body weight averaged 3 per cent below the Wistar norm, ranging from 8 per cent below to 4 per cent above normal.

Sections showed nothing abnormal in the renal cortex, with the exception of the usual slight infiltration by round cells, which appeared in four of the five rats in this group. In the pyramid, a slight amount of epithelial degeneration appeared in the papillary ducts in one case, and little in two others. In four cases, a small amount of fat (or lipid) was found in the pyramid, in the form of a few scattered droplets, some appearing in the epithelial cells and some in the interstitial tissue.

Group 10, on the Stock Diet—For additional normal controls, eight rats were taken from the normal stock colony. The diet used for maintenance of this colony was McCollum's diet I, composed of ground whole wheat 67.5 (parts by weight), casein 15, whole milk powder 10, butter fat 5.2, calcium carbonate 1.5 and sodium carbonate 0.8. In this group of normal rats, the body weight averaged 7 per cent above the Wistar norm, ranging from 13 per cent above to 8 per cent below normal.

In general, the kidneys in this group appeared histologically normal (table 2). Sections showed the usual slight infiltration by round cells in every case but one. In only five of the eight cases were slight amounts of fatty material found in the papilla and lower portion of the pyramid, but none in the cortex.

COMMENT AND CONCLUSIONS

RENAL INVOLVEMENT IN THE FAT-DEFICIENCY DISORDER

In the literature, mention of lesions of the kidneys is rarely made by the workers with fat-free diets, since complete autopsies on experimental animals have rarely been made. In most cases the diets actually contained small, but appreciable, amounts of fat. In the experiments of McAmis, Anderson and Mendel,⁶ however, the diets were sufficiently low in fats to give evidence of renal involvement, which was likewise noted by Burr and Burr.¹ These workers suspected that renal disorder is an important factor in the disease. This view is fully confirmed by the microscopic lesions found in the present study.

McAmis, Anderson and Mendel⁶ also (contrary to the observations in the present experiments) reported urinary calculi in three rats, but these three had been previously depleted of their store of vitamin A. A deficiency of this vitamin is known to produce urinary calculi (Van Leersum,⁷ McCarrison⁸). In the test rats of the present experiments, calcareofatty casts somewhat similar to those described by Van Leersum were found in the tubules of the kidneys, but they did not in any case result in vesical calculi.

Drummond and Coward⁹ obtained only normal conditions in rats on diets which they considered "devoid of true fats." They also made

6 McAmis, A. J., Anderson, W. E., and Mendel, L. B. Growth of Rats on "Fat-Free" Diets, *J. Biol. Chem.* **82** 247, 1929.

7 Van Leersum, E. C. Vitamin A Deficiency and Urolithiasis, *J. Biol. Chem.* **76** 137, 1928; **79** 461, 1928.

8 McCarrison, R. The Experimental Production of Stone in the Bladder, *Brit. M. J.* **1** 717, 1927; *Indian J. M. Research* **15** 197, 1927.

9 Drummond, J. C., and Coward, K. H. Nutrition and Growth on Diets Devoid of True Fats, *Lancet* **2** 698, 1921.

some autopsies, but reported no abnormal results. Their experiments, however, were continued for a relatively short period of time. Moreover, their diets were not strictly fat-free, since starch (which contains some nonextractable fat) was used in the diet, and the yeast (likewise fat-containing) was not extracted. In these experiments, as in those of Palmer and Kennedy¹⁰ and the earlier studies of Osborne and Mendel,¹¹ it is probable that the negative results were due chiefly to the small, but effective, amounts of fat contained in their diets.

OCCURRENCE OF RENAL FAT

We may conclude from the work of Traana,¹² Bell,² Smith¹³ and MacNider¹⁴ that fatty material can be demonstrated in normal renal epithelium, but the amount apparently varies greatly with species and age, and under different physiologic and pathologic conditions.

The results of the present study agree rather closely with those of Smith¹³ for normal rats. The kidneys of our normal control rats (stock animals, starch-fed rats and control group 6) showed practically no stainable fat (or lipid), except a few scattered droplets in the medulla. These droplets appeared both in the epithelial cells and in the interstitial tissue. Our test groups (except in cases with prolonged preservation in formaldehyde) usually showed considerable quantities of fat in the cells of both medulla and cortex, and this fat appeared to be associated in some degree with degenerative changes in the cells. In the abnormal controls (groups 7 and 8), fat was also demonstrable in the cortical cells, but was much less pronounced and more variable than in the test groups. In some of these cases no appearances of cellular degeneration were present. The appearance of fat in these cells may have represented the first indication of degeneration, or it may merely have represented a different "physiologic state" which was not present in the normal controls.

10 Palmer, L. S., and Kennedy, C. Fundamental Food Requirements for Growth of Rat. V. Influence of Fat in Diet, *Proc Soc Exper Biol & Med* **26** 427, 1929.

11 Osborne, T. B., and Mendel, L. B. Growth on Diets Poor in True Fats, *J Biol Chem* **45** 145, 1920.

12 Traana, R. Ueber das Verhalten des Fettes und der Zellgranula bei chronischem Marasmus und akuten Hungerszuständen, *Beitr z path Anat u z allg Path* **35** 1, 1904.

13 Smith, C. Lipoid Content of Kidney Tubule, *Am J Anat* **27** 69, 1920.

14 MacNider, W. de B. Concerning the Amount and Distribution of Stainable Lipoid Material in Renal Epithelium in Normal and Acutely Nephropathic Animals, with Observations on Functional Responses of the Kidney, *Proc Soc Exper Biol & Med* **19** 222, 1922.

CALCIFICATION AND OTHER DEGENERATIVE CHANGES

The description by Hueper¹⁵ of renal tubular degeneration, with subsequent calcification (due to hypercalcemia), agrees rather closely with the condition noted in the present study. In our series, however, there was no definite evidence that degenerative changes in the cortical cells always preceded calcification, but in the papillary region calcification appeared more definitely to follow cellular degeneration.

The calcium deposits in renal epithelial tubules described by Van Leeuwen⁷ (in vitamin A deficiency) also closely resemble those noted in the present study.

Pugh¹⁶ stated that in man the renal papillae may contain deposits of calcium in advanced age. In our study, however, age apparently is not an important factor in the process of calcification, since among the oldest animals of the entire series (groups 7 and 8 of the controls) no calcium deposits were found.

PROLIFERATION OF RENAL PELVIC EPITHELIUM

It is difficult to account for the proliferation of pelvic epithelium noted in many of the test animals. It is often associated with necrosis and calcification of the papilla (though not necessarily so), and may therefore be due in part to an irritative action of the necrotic mass in the renal pelvis.

In young rats that had died with xerophthalmia on diets deficient in vitamin A, Frontali¹⁷ observed that all showed a variable degree of cystitis, with metaplasia of the epidermic type, involving also the ureter and renal pelvis. Cystitis was never observed in our cases nor was an acute inflammation noted elsewhere in the kidney, except in the two cases mentioned. In these two instances, the infection was probably superimposed, since it was not found in the remaining cases.

Fujimaki and associates¹⁸ similarly found atypical metaplasia with keratosis in the urinary bladder and renal pelvis in rats suffering from a chronic deficiency of vitamin A. Renal calculi or metaplasia (keratinization) of the pelvic epithelium were likewise found by Wolbach and

15 Hueper, W. Metastatic Calcification in Organs of Dog After Injections of Parathyroid Extract, *Arch Path* **3** 14, 1927.

16 Pugh, W. S. Calcification in Kidney, *Internat J Med & Surg* **40** 288 1927.

17 Frontali, G. Infezione delle vie urinarie in carenza di vitamina A, *Riv di chir pediat* **24** 505, 1926.

18 Fujimaki, Y., Kimura, T., Wada, Y., and Shimada, S. Morphologic Changes of Pavement Epithelium of Albino Rats Fed on Vitamin A Deficient Diet. *Sei-I-Kwai M J* **46** 1, 1927.

Howe¹⁹ and by Tyson and Smith²⁰ in rats and guinea-pigs with vitamin A deficiency. In our experiments, however, no indication of cornification was found in the regions of proliferated epithelium. The epithelial hyperplasia noted in our series therefore appears to be different from the metaplasia (keratosis) produced by a deficiency of vitamin A.

EFFECT OF AMOUNT OF PROTEIN IN THE DIET

The various histologic lesions observed cannot be attributed to a diet high in protein as is evident by a comparison of the results in the various groups (table 2). As a matter of fact, in rats 23, 24, 26, 27 and 28 in group 2 (on diet 550 throughout, a diet high in protein), the lesions usually appeared less numerous and severe than in most of the rats maintained throughout on diet 550 B, which was low in protein (all of group 3, rats 47 to 51 of group 4, rats 58 to 86 of group 5 and rats 91 to 95 of group 6). On the whole, it appears improbable that the level of the dietary protein (ranging from 12 to 24 per cent) in these experiments had any appreciable effect on the incidence of the renal lesions observed.

SUMMARY

Characteristic renal lesions have been demonstrated in rats reared on Burr's highly purified diets, which are practically fat-free, but otherwise adequate.

The most striking and characteristic renal lesion is the calcification in the cells of some renal tubules and in necrotic areas of the renal medulla. In extreme cases there is complete disintegration of the apical region of the pyramid.

Various forms of renal epithelial degeneration and fatty or lipoidal changes also occur to a variable extent. These may or may not be associated with the calcification.

In the medulla, large quantities of fatty or albuminous material may accumulate, forming casts in the lumina of the tubules and especially in the papillary ducts.

An atypical (uncornified) hyperplasia is often found in the renal pelvic epithelium. This usually appears most pronounced where necrosis of the papilla is also present.

Slight focal infiltration by round cells is found in the test rats, but no more frequently than in the normal controls.

19 Wolbach, S. B., and Howe, P. R. The Epithelial Tissues in Experimental Xerophthalmia. *Proc. Soc. Exper. Biol. & Med.* **22**: 402, 1925; Vitamin A Deficiency in the Guinea-Pig, *Arch. Path.* **5**: 239, 1928.

20 Tyson, M. D., and Smith, A. H. Tissue Changes Associated with Vitamin A Deficiency in the Rat, *Am. J. Path.* **5**: 57, 1929.

The inclusion bodies incidentally noted in the cortical epithelium of some of the controls apparently have no relation to the disorder caused by a deficiency of fat in the diet

The addition of from 2 to 20 per cent of lard, or of slight amounts of cod liver oil, to the diet usually prevents or cures the renal disorder, at least to a large extent. Especially the calcareous degeneration and casts are almost completely eliminated. Various other types of fat (such as corn oil, olive oil and methyl linolate) usually appear somewhat less beneficial to the kidney, in which some of the lesions persist, although the general condition of the body is cured or greatly improved.

The concentration of dietary protein, within the range used, shows no definite relation to the incidence or to the severity of the renal lesions observed.

IODINE DEFICIENCY AND GOITER

INFLUENCE OF A DIET POOR IN IODINE ON THE THYROID GLAND IN WHITE RATS

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WICHITA, KAN

Chatin's¹ theory that endemic goiter is the result of a deficiency of iodine is accepted by most American scientists. In mapping the areas of the United States in which goiter is prevalent, McClendon and Hathaway² determined the iodine content of foodstuffs and water from goitrous and nongoitrous areas, and showed that there is little iodine in the vegetables and the waters of those parts of the United States in which simple goiter is a serious problem.

Marine and Lenhart³ who studied extensively the effect of iodine on the mammalian thyroid gland, arrived at the conclusion that this gland undergoes hyperplasia whenever its iodine content falls below 0.1 per cent, and that the therapeutic effects of iodine are the result of restoring to the thyroid gland the normal amount of iodine.

A direct experimental proof for the theory of Chatin has never been attempted in this country. In southern Germany Tanabe⁴ succeeded in producing hyperplasia of the thyroid gland by giving white rats a diet poor in iodine. Freiburg being situated, however, in a district where goiter is endemic, Tanabe's positive results must be regarded with great caution, since it is well known that in goitrous areas, domesticated animals incur hyperplasia of the thyroid gland spontaneously. Tanabe's successful experiments have to be repeated in a goiter-free country before they can be accepted as proof for the iodine-deficiency theory.

Wichita, Kan., is free from endemic goiter. There arises the question whether or not Tanabe's experiments would turn out to be positive also in this locality.

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1 Chatin. Recherche de l'iode dans l'air, les eaux, le sol et les produits alimentaires des Alpes de la France et du Piémont, *Compt. rend.*, Paris **33** 529 and **34** 14 and 51, 1851-1853.

2 McClendon, J. F., and Hathaway, J. C. Inverse Relation Between Iodine in Food and Drink and Goiter, Simple and Exophthalmic, *J. A. M. A.* **82** 1668, 1924.

3 Marine, D., and Lenhart, C. H. Relation of Iodine to the Structure of Human Thyroids, *Arch. Int. Med.* **4** 440, 1909.

4 Tanabe. Experimenteller Beitrag zur Aetiologie des Kropfes, *Beitr. z. path. Anat. u. z. allg. Path.* **73** 415, 1925.

EXPERIMENTS

The first series of experiments was begun in April, 1929, with two litters of young white rats, one being 12, the other 20, weeks old. The experimental lot consisted of five animals, three taken from the younger and two from the older litter. These white rats received food poor in iodine as outlined by Tanabe⁵; each was given daily from 8 to 10 Gm of barley and distilled water, and every third day from 2 to 3 Gm of uncooked meat and 2 Gm of fresh lettuce. The remaining five animals from the same litters were kept as controls and were fed on a properly balanced diet and fresh city water.

The cages were kept scrupulously clean, to avoid any possible influence of filth and fecal material on the thyroid gland as pointed out by Sasaki⁵ and McCarrison⁶. The floors of the cages were made of mesh wire, and no hay or other material was used for bedding.

The feeding was continued for a period of 119 days, and both lots of rats were killed with chloroform. The thyroid glands were dissected immediately after death, measured and preserved in a diluted solution of formaldehyde (1:10). Postmortem changes were thus prevented. No constitutional differences were noticed between the two experimental lots. The macroscopic and microscopic observations in the thyroid glands are given in tables 1 and 2.

I was unable to find any striking differences between the two groups of white rats. In the experiments described, a diet poor in iodine failed to produce the changes which Tanabe was able to see. The average body weight of the controls being 170 Gm, their thyroid lobes measured, on the average, left 5.3 by 3.1 by 2.2 mm, right, 5 by 3.4 by 2.6 mm. After a diet poor in iodine the average body weight was 132 Gm and the average size of the thyroid lobes was as follows: left 5.4 by 3.4 by 1.9 mm, right, 4.5 by 3 by 1.8 mm. Both groups therefore presented the same normal size that Wegelin described in white rats from goiter-free regions of Germany.

Early goiter in animals manifests itself in the small size of the acini, decrease of the colloid and columnar size of the epithelium, with formation of papilli and mitotic figures, and in hyperemia of the gland. Not one of these typical changes occurred in our animals after a diet poor in iodine. Their glands showed even a slightly more viscous colloid and lower epithelial cells than those of the controls (fig. 1).

⁵ Sasaki. Zur experimentellen Erzeugung der Struma, *Deutsche Ztschr. f. Chir.*, 1912, vol. 119, cited from Wegelin in Henke and Lubarsch. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 8, p. 545.

⁶ McCarrison. *The Thyroid Gland in Health and Disease*, London, William Wood & Company, 1917. Report on the Etiology and Epidemiology of Endemic Goiter, *Compt. rend. Conference internat. du goitre*, Berne, 1927.

TABLE 1—Controls Receiving Well Balanced Diet

White Rat	Sex	Weight, Gm	Size of Thyroid Gland, Mm	Acini	Colloid	Epithelium	Fibrous Tissue	Blood Vessels	Lymph Spaces	Desquamation	Tracheal Leukocyte infiltration of mucosa
1	M	172	L 4×3×1 R 5×3×2	Most medium sized, slightly larger in periphery, 15 acini appear without lumen	Well stained, filling one half to three fourths of each lumen, few acini contain unstained colloid	Cuboid in center slightly smaller in periphery, occasionally pin-pointation of wall in peripheral acini	Very scanty	Many well filled capillaries	Empty	None	
2	F	177	L 5.5×3×2.5 R 5.1×4×3	Small in center, with 55 to 40 solid medium sized in periphery very few larger	Thin colloid, filling half of each lumen, few empty acini	Cuboid in most of the acini few pyknotic nuclei, few desquamated cells	Very scanty	Capillaries well filled	Empty	Occasionally few single cells	Epithelium well preserved
3	M	152	L 6×4×2.5 R 5×3×2	Medium sized in center, slightly larger in periphery, 15 to 20 appear solid	Thin colloid, filling third to half of each lumen	Cuboid, no degenerative changes, no desquamation	Very scanty	Capillaries poorly filled	Empty	Ten cells	One side of epithelium evaginated
4	F	219	L 6×4×2 R 5×4×1	Medium sized in center, larger in periphery, about 18 with out lumen	Well stained colloid, filling three fourths of each lumen, few acini empty	Cuboid in center slightly lower in periphery occasionally papillae in the larger peripheral acini	Very scanty	Capillaries well filled	Empty	In about 20 acini a few cells	Leukocyte infiltration of mucosa
5	M	190	L 5×3×3 R 5×2×3	Small and medium sized in center, few large ones in periphery, 8 to 10 of each lobe, with out lumen	Thin colloid with large vacuoli, filling third to half of each lumen, very few acini completely filled	Cuboid in center and in periphery no papillae in totic figures	Very scanty	Well filled capillaries	In few lymph spaces, colloid like in interstitium	None	Normal, well preserved mucosa

TABLE 2—*Experimental Series 2, Fed Barley and Distilled Water, with Every Third Day 2 Gm of Lettuce and Meat, for 119 Days*

White Rat	Sex	Weight, Gm	Size of Thyroid Gland, Mm	Aeoi	Colloid	Epithelium	Fibrous Tissue	Blood Vessels	Lymph Spaces	Disquamation	Trachea
1	F	181	L 6×4×2 R 5×3×2	Medium sized in center, very large in periphery, 3 to 4 aeoi solid	Densely stained, filling lumen three fourths or completely, no empty aeoi	Flat, cuboid in center, flatter in periphery, no mitotic figures, no degenerative changes of the nuclei	Very scanty	Capillaries moderately filled	Colloid like in lumen in few	None	Well preserved, normal mucosa
2	M	143	L 5×3×1.5 R 5×3×1.5	Medium sized in center, many larger in periphery, none solid	Densely stained, filling most of the aeoi completely no empty aeoi	Flat, cuboid, no mitotic figures, no degenerative changes	Very scanty	Some capillaries well filled	Colloid like material in few	None	Intention of epithelium
3	M	164	L 5×3×2 R 6×4×2	Small and medium sized in center, none large, 15 to 18 solid	Densely stained, filling most of aeoi completely, no vacuoli	Flat, cuboid, no papillae, no mitotic figures	Very scanty	Capillaries poorly filled	Colloid like material in few	None	Epithelium well preserved
4	F	123	L 6×4×2 R 6×3×2	Small and medium sized in center, larger in periphery, about 17 solid	Not thick, filling lumen three fourths or completely occasion ally empty aeoi	Cuboid in center, lower in periphery, few papillae	Very scanty	Capillaries very well filled	Colloid like material in very few	None	Part of epithelium exfoliated
5	M	79	L 5×3×2 R 5×2×1.5	Medium sized in center, small in isthmus, many large in periphery, 15 with out lumen	Well stained collod, filling three fourths of each lumen, no empty aeoi	Mostly cuboid, slightly lower in periphery, no no papillae, no mitotic figures	Distinct fibrous septums	Capillaries not filled larger vessels contain much blood	Imply	None	Intention of mucosa

After this unsuccessful attempt to confirm Tanabe's results, the experimental conditions were made more severe. Lettuce was excluded from the food completely, since green leaves constitute the most important source of iodine intake. This second experiment was carried out on five young white rats, their food consisting exclusively of barley and distilled water. This feeding was continued with the same individuals

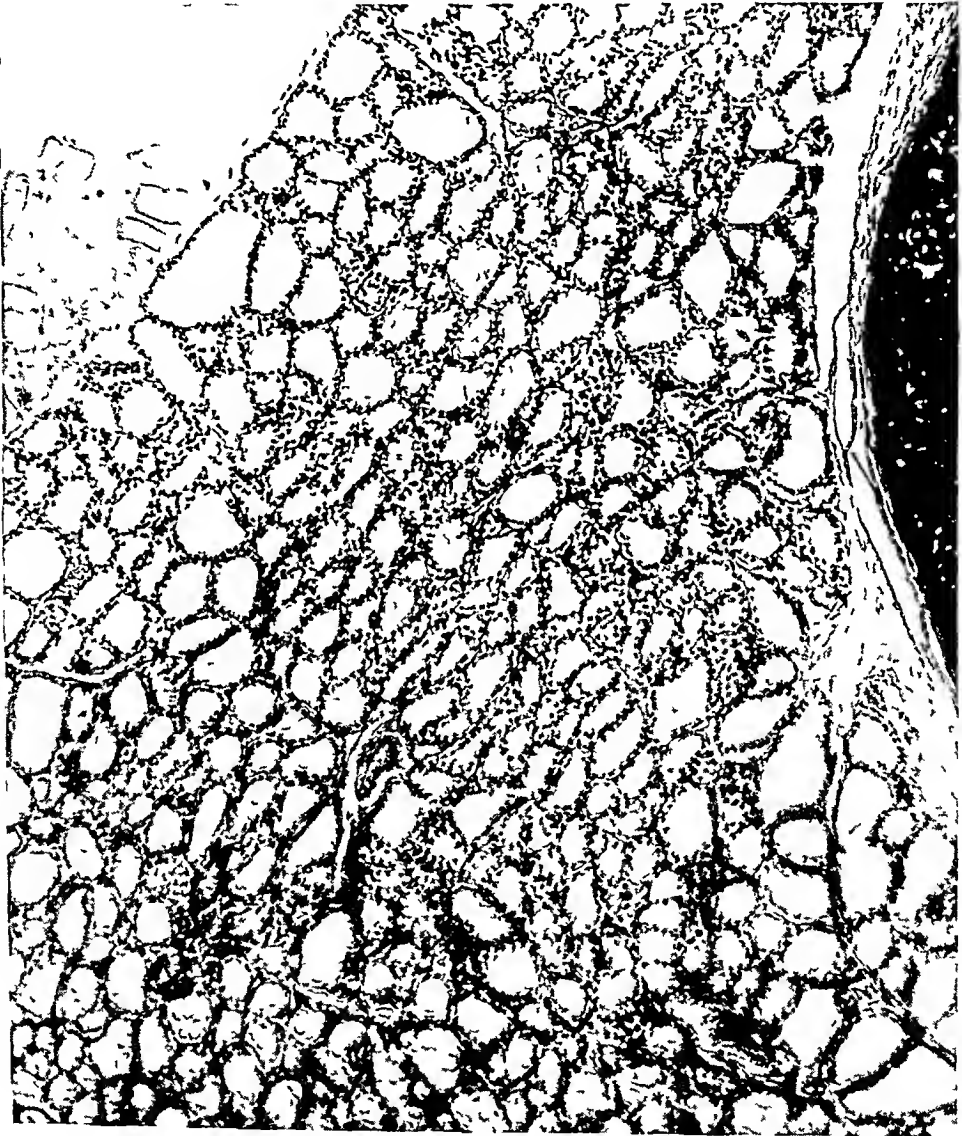


Fig 1—Normal thyroid gland of the white rat (control series 1)

for a period of 90 days. But even this strict iodine-free diet failed to cause any enlargement of the thyroid gland. On the contrary, all the animals of this series showed definitely smaller glands than the controls, not only absolutely, but also relative to their body weight. The five animals, after being chloroformed to death, weighed, on the average, 152 Gm, the average size of the left lobe was 4.4 by 1.9 by 2.2 mm; of the right, 4.6 by 2.2 by 2.4 mm. Microscopically, these glands

presented signs of atrophy the follicles being small and filled with intensely stained colloid, the epithelium was low, and the capillaries were poorly filled with blood (table 3 and fig 2) Thereafter, a prolonged attempt was made with the same diet on four other rats, and the feeding was continued over a period of 160 days In all these four animals identical changes occurred, namely, a still more pronounced atrophy of the thyroid gland The average body weight of these four animals was 125 Gm, the average size of the left lobe was 4.7 by 2 by 1.8 mm, that of the right, 4.7 by 2.2 by 1.8 mm The microscopic examination revealed small acini with very viscous colloid, a low epithelial cell layer and poor filling of the capillaries with blood (table 4)

The completely negative results of my three experiments, which were instituted under even stricter conditions than those of Tanabe, are surely not in favor of the generally accepted theory that hyperplasias of the thyroid gland, including endemic goiter, are due to insufficiency of iodine in the diet of the individuals My observations, on the contrary, make it clear that a diet poor in iodine produces atrophy of the thyroid gland, the severity of which is in inverse proportion to the amount of iodine taken and in direct proportion to the length of time the feeding experiments are continued My results confirm the view held by Wegelin, that endemic goiter cannot be explained as compensatory hypertrophy of the thyroid gland, due to a low content of iodine in the food, but rather that, in insufficiency of iodine, atrophy of the organ must be expected, since iodine is a strong stimulant to the action of the thyroid gland

Without questioning the important rôle that sufficiency of iodine may play in the prevention of goiter, I am led to the belief that the essential cause of goiter is a positive agent As one of the possible positive factors, a high content of calcium in the drinking water is held responsible by several investigators for the development of goiter McClelland,⁷ Bouchardat,⁸ Billiet,⁹ Boussingault¹⁰ and Pighoni¹¹ advanced the theory that an excess of calcium sulphate or carbonate

7 McClelland On the Connection Between Goiter and Cretinism, Their Nature and Causes in Some Inquiries in the Province of Kemaon Relative to Geology and Other Branches of Natural Science, Including an Inquiry into the Causes of Goiter, Calcutta 1835, Dublin J M Sc **11** 295, 1837

8 Bouchardat De l'influence de la qualite des eaux sur la production du goitre et du cretinisme, Bull de l'Acad nat de med, 1851, cited from Wegelin (footnote 5, p 537)

9 Billiet. Observations sur le recensement des personnes atteintes de cretinisme Ann d'hyg 1853, vol 50, cited from Wegelin (footnote 5, p 538)

10 Boussingault Memoires sur les salines iodiferes des Andes, Ann de chim et de phys, vol 54, cited from Wegelin (footnote 5 p 538)

11 Pighoni Ricerche sulla endemia gozzo-cretinica nella regione veneto-lombarda e nella provincia di Reggio-Emilia, Riv sper di freniat **44** 66, 1920

TABLE 3—*Experimental Series 3, Fed Bailey and Distilled Water for Ninety Days*

White Rat	Sex	Weight, Gm	Size of Thyroid Gland, mm	Adm	Colloid	Epithelium	Fibrous Tissue	Blood Vessels	Lymph Spaces	Disquamation	Trachea
1	M	80	L 1x2x1.5 R 1x2x1.5	Most small sized, in periphery several medium sized 1 or 5 solid	Densely stained, filling lumen three fourths or completely	Cuboid and low cuboid, no papillae, no mitotic figures	Very scanty	Capillaries very poorly filled, larger vessels well filled	Filled with colloid like material	In few vessels	Very well preserved mucosa
2	F	137	L 1.5x2x3 R 1.5x2x2	Small and medium sized in center, slightly larger in periphery, 4 or 5 solid	Well stained, filling of each lumen three fourths	Low cuboid, no papillae, no degenerative changes, no mitotic figures	Very scanty	Capillaries not filled, larger vessels moderately filled	Well filled with colloid like material	None	Well preserved mucosa
3	M	220	L 4x2x3 R 1x2x3	Small in center, medium sized in periphery, 6 to 8 solid	Well stained, filling lumen three fourths or wholly	Cuboid and low cuboid, no proliferative changes	Very scanty	Capillaries not filled, larger vessels well filled	Well filled	None	Well preserved mucosa
4	M	137	L 5x2x2 R 5x1.5x2.5	Small in center, occasionally medium sized in periphery	Well stained, filling acini only about one fourth full	Cuboid and low cuboid, no papillae	Very scanty	Capillaries not filled, larger vessels well filled	Well filled	None	Well preserved mucosa
5	F	117	L 1x1.5x2 R 4.5x1.5x2	Small and medium sized, very few larger	Thin and moderately viscous, filling more than half of each lumen	Low cuboid, no proliferation, no mitotic figures	Very scanty	Capillaries not filled, larger vessels well filled	Well filled	None	Well preserved epithelium, marked lymphocytic infiltration
								Capillaries not filled, larger vessels moderately filled	Well filled	None	Well preserved epithelium, marked lymphocytic infiltration

TABLE 4—*Experimental Series 4, Fed Barley and Distilled Water for 160 Days*

White Rat	Sex	Weight, Gm	Size of Thyroid Gland, Mm	Veins	Colloid	Epithelium	Interstitial Tissue	Blood Vessels	Lymphatics	Desquamation	Trachea
1	M	80	L 4×2×2 R 4×1.5×2	Small in center, medium sized in periphery, 1 to 3 solid	Most of acini empty, thin colloid in few peripheral ones	Cuboid, nucleoli pyknotic in many cells	Very scanty	Very strongly filled	Empty	Extensive	Epithelium not well preserved
2	F	119	L 4.5×2×1.5 R 4.5×2×2	Small, in periphery, few larger, 3 solid	Very dense, completely filling most of the acini	Low cuboid epithelium, no mitotic figures	Very scanty	Capillaries well filled	Empty	None	Well preserved epithelium
3	F	134	L 5×2.5×3 R 4.5×2×2	Small in periphery, some medium sized, 10 solid	Thin colloid filling most of acini, in peripheral acini, only part of each lumen filled	Cuboid, no epithelium, no mitotic figures	Very scanty	Capillaries well filled	Empty	None	Well preserved epithelium
4	M	122	L 4.5×2×1 R 5×2×1.5	Most small, 5 or 1 solid	Densely stained, filling most of acini	Cuboid and low cuboid epithelium	Very scanty	Very well filled capillaries	Empty	None	Well preserved epithelium

may cause endemic goiter. In a recent paper, Kottmann¹² pointed out that calcium decreases the dispersity of the blood serum and increases the viscosity of the thyroid colloid. Abeln¹³ was able to demonstrate in experiments on white rats that an excess of calcium lowers the

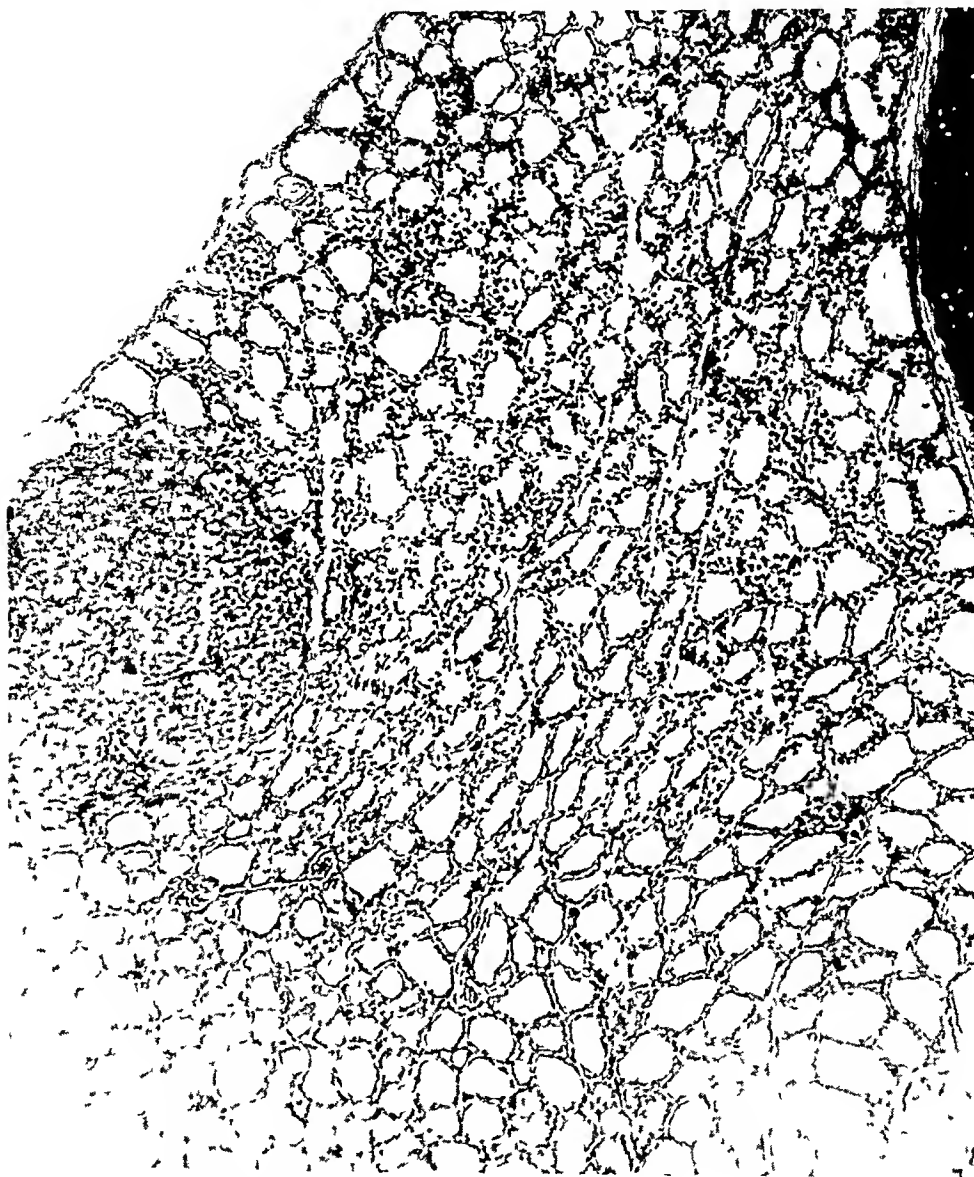


Fig 2—Thyroid gland after iodine-free diet for ninety days (experimental series 3)

12 Kottmann. Kolloidchemische Untersuchungen über Schilddrüsenprobleme, Schweiz med Wchnschr 50 644, 1920

13 Abeln, I. Schilddrüse und Mineralstoffwechsel. Einfluss des Dinatriumphosphats und der Kalziumsalze auf die Wirkung der Schilddruesensubstanzen. Biochem Ztschr 72 199, 1928

metabolic action of thyroxine. Wilms¹⁴ and Répin¹⁵ observed that water from goitrous districts will lose its activity after precipitation of its calcium by boiling. Geologic studies are also in favor of this theory. McCarrison,⁶ in his analysis of conditions in the goitrous regions of Chival and Gilgit in northern India, found that there are certain large

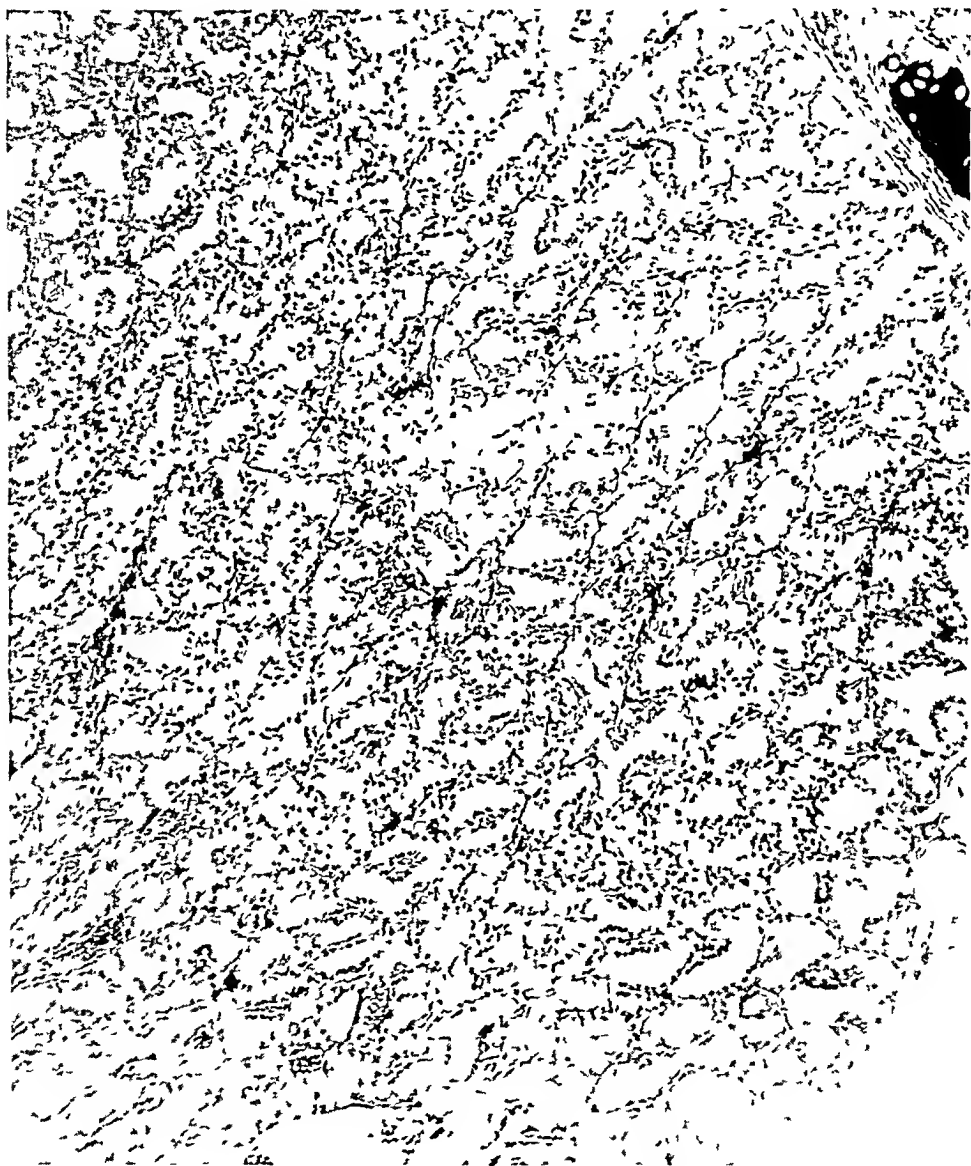


Fig 3—Hyperplastic goiter after diet rich in calcium and free from iodine for eighty-five days (experimental series 5)

outcrops of limestone, and that it is from these that the villages in which goiter is most prevalent derive their supply of water.

14 Wilms. Ursache und experimentelle Erzeugung des Kropfes, *Zentralbl f Chir*, 1910, vol 37, no 31, Ursache und experimentelle Erzeugung des Kropfes, *Deutsche med Wchnschr* 36 604, 1910

15 Répin. Les eaux goitrigenes. *Rev d'hyg* 33 317 1911

Also from Tanabe's recent experiments in the Institut of Aschoff it appears that diets high in calcium and, at the same time, low in iodine produce the most pronounced hyperplasias of the thyroid gland

I studied the influence of drinking water rich in calcium on eight young rats. They were fed only barley and as drinking water a pure

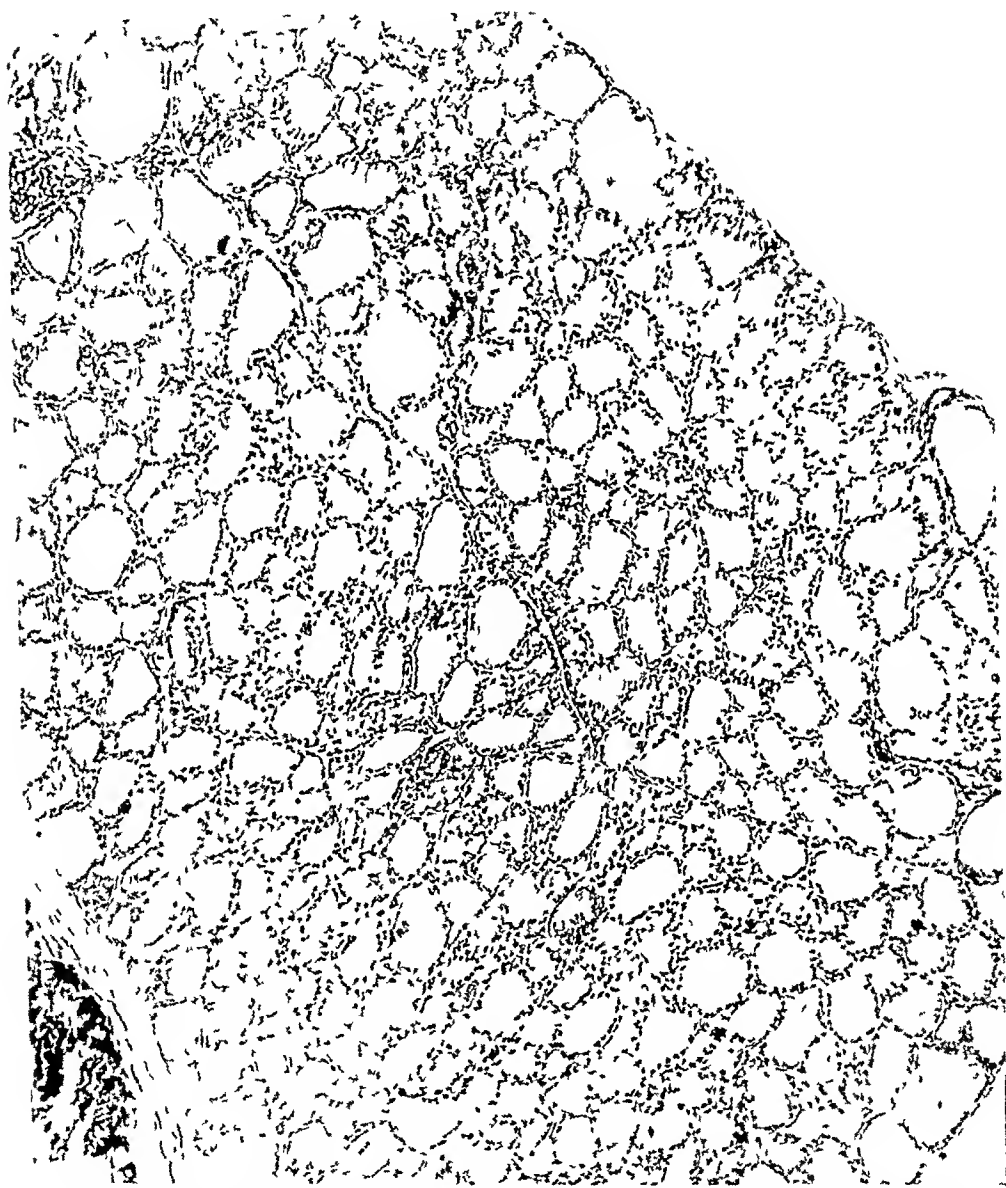


Fig 4—Small colloid goiter after a diet rich in calcium and iodine for seventy days (experimental series 6)

2 per cent solution of calcium chloride. After a period of ninety days, five of these animals were killed with chloroform and their thyroid glands examined. The observations were uniform in all. The thyroid glands were distinctly enlarged and appeared very hyperemic. The average weight of this series being 158 Gm, the average size of the thyroid lobes was as follows: right, 5.6 by 2.3 by 3.5 mm, left 6 by

TABLE 5—*Experimental Series 5, Fed Bailey and Calcium-Rich Water for Eighty-Five Days*

White Rat	Sex	Weight, Gm	Size of Thyroid Gland, Mm	Aeini	Colloid	Epithelium	Fibrous Tissue	Blood Vessels	Lymph Spaces	Desqua- mation	Trachea
1	M	110	L 6×3×2 R 6×3×2	Narrow tubules, with papilla- tions very many solid	Most of aeini empty, in few, central small globule of dark colloid	High columnar with plications and papillae, occasionally, mitotic figures	Very scanty	Capillaries much dilated and well filled	Empty	None	Well preserved epithelium, round cells in submucosa
2	F	182	L 6×3×4 R 6×4×4	Elongated, nar- row tubules with papilla- tions, few solid	Most of aeini empty, granular colloid in few	Columnar, with papillae, no mitotic figures, few large, dark nuclei	Very scanty	Hypereemie	Empty	None	Well preserved epithelium
3	F	122	L 6×3×2.5 R 5.5×2×3.5	Smallest and smallest	Most of aeini appear empty, granular colloid in few	High cuboid, no papillae	Very scanty	Hypereemie	Empty	None	Well preserved epithelium
4	F	110	L 6×2.5×3 R 5.5×2×3.5	Narrow tubules, irregular in form, 6 to 8 solid	Most of aeini empty, very thin colloid in few	High cuboid in several aeini, papillae, occasional- ly, very large nuclei, no mitotic figures	Very scanty	Hypereemie	Empty	None	Well preserved epithelium
5	M	118	L 6×2×3 R 5.5×2×3	Narrow tubules of irregular form, 3 to 4 solid	Aeini empty	Columnar epithe- lium with papillae in peripheral aeini	Very scanty	Well filled	Containing some colloid like material	None	Well preserved epithelium

TABLE 6—*Experimental Series 6, Fed Calcium-Rich Water, with Well Balanced Diet for Seventy Days*

White Rat	Sex	Weight, Gm	Size of Thyroid Gland, Mm	Aeini	Colloid	Epithelium	Fibrous Tissue	Blood Vessels	Lymph Spaces	Desqua- mation	Trachea
1	F	90	L 4×1.5×2 R 5.5×2×2	Large in periph- ery, medium sized and small in center, none solid	Well stained, filling most of aeini completely	Low cuboid, no papillae	Very scanty	Moderately filled	Several filled with blood	Extensive	Leukoeytic infiltration
2	F	170	L 7×2×2 R 6.5×3×1.5	Middle sized in center, larger in periphery, none solid	Densely stained, filling most of aeini completely	Cuboid in few peripheral aeini, papillae	Very scanty	Capillaries moderately filled, larger vessels well filled	Empty	None	Well pre- served no inflammation
3	F	120	L 6×3×1.5 R 6×3×1.5	Middle sized and small in center, few larger in periphery	Very thin or unstained in many aeini, well stained in peripheral aeini	Cuboid no mitotic figures, no papillae	Very scanty	Extensively hypereemie	Not filled	None	Well preserved

2.9 by 2.9 mm. In their microscopic picture all five thyroid glands presented a marked epithelial hyperplasia. The acini formed elongated narrow tubules with high columnar cells, the walls formed infoldings and plications, the colloid did not stain at all or very faintly, and many acini appeared solid. The blood vessels were much dilated, the capillaries between the acini contained a great amount of blood. Thus the histologic changes corresponded completely to the description which Langhans and Wegelin,¹⁶ and Marine and Lenhart³ gave of the mammalian hyperplastic goiter (table 5 and fig. 3).

Three of the eight animals were kept alive for another period of seventy days, the water rich in calcium being given to them but the diet poor in iodine being replaced by a well balanced one, with plenty of green vegetables. After 70 days, these animals still showed a definite enlargement of the thyroid glands, but without hyperemia. The average body weight in this series was 145 Gm., the average size of the thyroid glands was right, 6.3 by 3 by 1.5 mm., left, 6.5 by 2.2 by 1.8 mm. Histologic examination revealed large acini with cuboid epithelium, the colloid stained densely, the blood vessels were only moderately filled with blood. Several lymph spaces between the acini contained material that stained like colloid. These glands represented, therefore, small goiters of the colloid type (table 6 and fig. 4).

The last experimental results conform to the work of McCarrison,⁶ who produced small colloid goiters by a diet rich in calcium, but otherwise well balanced.

That an excess of iodine in the drinking water exerts an inhibitory action on hyperplasia of the thyroid gland—in spite of a high content of calcium—was demonstrated clearly by Tanabe.⁴

COMMENT

In table 7, the average size of the thyroid glands and the average body weight of each experimental series are tabulated. From the negative results of my attempt to produce goiter by means of an insufficiency of iodine in the food inferences may be drawn that lack of iodine is neither the only nor the essential cause of endemic goiter. The positive results of the second experimental series with a diet rich in calcium indicate that a positive agent is responsible for the development of goiter. This positive agent may not be a single specific factor, and this or these positive agents may not alone cause hypertrophy of the thyroid gland in the presence of a high amount of iodine in the food nor may insufficiency of iodine in itself cause endemic goiter in the absence of the other agents that cause goiter, but when both are present the conditions for the development of hyperplastic goiter seem to be at their optimum. Only by this conception of the etiology of goiter

¹⁶ Langhans and Wegelin. *Der Kropf der weissen Ratte*, Bern, Paul Haupt, 1919.

is one able to understand why endemic goiter may be present in localities rich in iodine, and, on the other hand, absent in regions poor in iodine

The last experimental series in which hyperplastic goiter was produced with a diet rich in calcium and poor in iodine and colloid goiter with a diet rich in calcium and iodine are not in favor of McCarrison's theory that these two types of goiter are entirely different from the etiologic standpoint, but indicate that the different structure of the thyroid gland depends on the amount of iodine in the food, the essential cause of the enlargement in each case being identical

Comparative studies, made in Europe following a suggestion of Aschoff, have shown that the histologic structure of goiters varies according to the part of the country in which they occur. In certain regions, especially in level regions, the diffuse colloid goiter with and without hyperthyroidism, and exophthalmic goiter predominate. In

TABLE 7—Average Weight of Animals and Average Size of Thyroid Glands in All Six Experimental Series

Series	Diet	Duration, Days	Weight, Gm	Right Lobe, Mm	Left Lobe, Mm
1	Mixed diet	119	170	5×3.4×2.6	5.4×3.1×2.2
2	Barley, distilled water, every few days lettuce, meat	119	182	5.4×3×1.8	5.4×3.4×1.9
3	Barley and distilled water	90	152	4.5×2.6×2.3	4.4×1.9×2.2
4	Barley and distilled water	160	125	4.7×2×1.8	4.7×2.2×1.8
5	Barley and 2% calcium chloride	85	158	5.6×2.3×3.5	6×2.9×2.9
6	Mixed diet and 2% calcium chloride	70	145	6.3×3×1.5	6.5×2.2×1.8

more mountainous countries the toxic goiter is an exception, and the nearer one approaches the center of the endemic area the less one meets with the colloid goiter. It is replaced by the colloid-poor, diffuse parenchymatous goiter in childhood and by the adenomatous parenchymatous nodular goiter with its degenerative forms in adults. It can hardly be doubted that, as in my last experimental series, these differences in the architecture of the goiters are due to differences in the iodine content of the food, the positive etiologic factor, hitherto unknown, being the same and being world-wide.

SUMMARY

Attempts to produce goiter in white rats by feeding a diet poor in iodine gave only negative results.

Excess of calcium in the drinking water and a low intake of iodine caused a marked epithelial hyperplasia of the thyroid gland.

Drinking water rich in calcium and a diet rich in iodine produced small colloid goiters.

Insufficiency of iodine was shown not to be the essential cause of goiter.

THE EFFECT OF EXPOSURE TO AN ULTRAHIGH FREQUENCY FIELD ON GROWTH AND ON REPRODUCTION IN THE WHITE RAT*

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Since the development of a high frequency oscillator for the production of artificial fever in man,¹ it has become of increasing importance to know the biologic reactions produced by such an agent. Christie and Loomis,² and Kahler, Chalkley and Voegtlin³ expressed the belief that the effect of a high frequency field depends primarily on the production of a rise in temperature in the organism, while Schereschewsky⁴ stated that certain wave lengths (from 15 to 38 meters) exert a specific effect on living cells. An investigation was accordingly planned to determine the effect of exposure to a high frequency field on growth and reproduction in the white rat.

The high frequency oscillator used in these experiments was constructed on the same principle as a short wave radio transmitter, with the exception that the energy is concentrated between two condenser plates instead of being directed from an aerial. The heater was designed by the General Electric Company⁵ and consists of a vacuum tube oscillator and rectifier that supplies the high voltage for the oscillator. The high frequency oscillator is composed of two 75 watt radiotrons operating at a frequency of from 9,000 to 12,000 kilocycles. An air-cooled transformer having a 4,500 volt secondary and feeding a full wave rectifier forms the 2,000 volt direct current plate supply for the oscillator.

Young white rats weaned at 28 days of age and weighing from 40 to 55 Gm were used in these experiments. There were two different series of experiments, one of which was carried out in the early part of 1929 and the other in the early part of 1930.

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* From the Department of Biochemistry, Union University Medical Department, Albany Medical College

1 Carpenter, C M, and Page, A B. *Science* **71** 450, 1930

2 Christie, R V, and Loomis, A L. *J Exper Med* **49** 303, 1929

3 Kahler, H, Chalkley, H W, and Voegtlin, C. *Pub Health Rep* **44** 339, 1929

4 Schereschewsky, J W. *Pub Health Rep* **41** 1939, 1926

5 Dr W R Whitney of the General Electric Company placed the apparatus at our disposal and members of his research staff, particularly A B Page and K C DeWalt, gave technical assistance from time to time

In the first series of experiments there were six male and eight female rats. These rats were put on the Sherman diet B,⁶ which was used at that time as our stock ration diet. The rats were divided into two groups so that litter mates were evenly distributed in each group, and one of the groups was exposed to a high frequency field while the other was kept as control. The high frequency exposure was given five days a week over a period of from sixty to ninety days. The length of each treatment for the first two weeks was thirty minutes, and then it was increased to forty-five minutes. The rats were heated each day to a rectal temperature of from 39.4 to 40.5 C and kept in that range for from fifteen

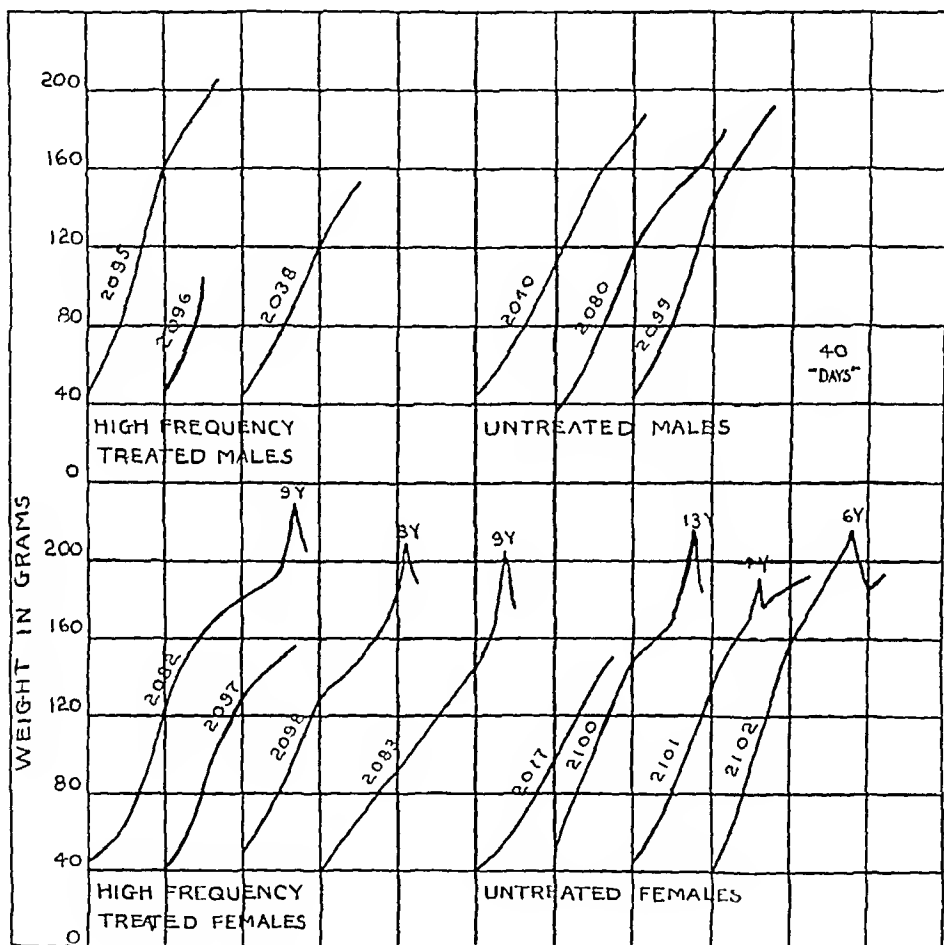


Chart 1—Experiments of the 1929 series showing the effect on growth of exposure of rats to ultrahigh frequency field. Rats in this series were fed on Sherman's diet B.

to thirty minutes. The normal rectal temperature of the rats varied from 37 to 37.5 C. Our plan was to heat the rats to the required temperature in from fifteen to twenty minutes, and then maintain them at that temperature. It was difficult to keep the rats at any set temperature, and it was necessary to record the rectal temperatures at intervals of from fifteen to twenty minutes in order to adjust the distance of the plates to keep the rats from getting either too warm

or too cool. The results of this group of experiments on growth are plotted in chart 1. A summary of the young born and reared by the heated and unheated mother rats in both series of experiments is given in the table.

In the second, or 1930, series of experiments, there were fourteen rats. The seven males were litter mates, four of which were given high frequency treatment and three kept as controls. The seven females were also litter mates, four being given treatment and three kept as controls. These rats were all put on Bills' modification⁷ of Steenbock's stock diet, which we adopted in this laboratory in the summer of 1929, and have found very satisfactory. The second series of rats were also treated five days a week over a period of from ninety to one hundred

Effect of Repeated Exposure to High Frequency Field on Reproduction and Rearing of Young

Experiment Series	Rat Number	High Frequency Exposure	Age at Birth of First Litter, Days	Number in Litter	Number Weaned at 25 Days of Age	Average Weight of Young at Weaning, Gm.	Comment
1929	2082	Treated	132	9	6	43	No litter during period of observation
	2097	Treated					
	2098	Treated	114	8	8	42	
	2083	Treated	122	9	6	45	
1929	2077	Untreated					No litter during period of observation
	2100	Untreated	96	13	9	47	
	2101	Untreated	92	7	2	47	
	2102	Untreated	98	6	4	46	
1930	2385	Treated	146	13	8	47	Rat developed infection and young died at 4 days of age. Died after sixth treatment from too high temperature.
	2386	Treated	146	8	0		
	2387	Treated					
	2388	Treated	155	8	6	44	
1930	2389	Untreated	117	11	8	44	
	2390	Untreated	116	10	7	50	
	2391	Untreated	123	9	6	54	

and twenty days. The length of each treatment in this series was increased to one hour, and the temperature was brought up to from 40.2 to 40.5 C in the first half hour and then maintained at that temperature for the next half hour. Occasionally, the temperature rose to 41.6 C, and in one instance five of the seven rats were heated to a temperature of from 43.3 to 43.9 C. One of the rats in this group died. The female rats in this series were not mated until they were 90 days of age. The growth curves of these rats are plotted in chart 2 and the table contains the record of young born and reared by the mother rats of this series.

We realize that the number of rats used in these two series of experiments is too few to draw any sweeping conclusions, but nevertheless they do show several interesting points. One reason for using

⁷ Bills, C. E., Honeywell, E. M., and MacNair, W. A. J. Biol. Chem. 76: 251, 1928.

so few animals is that we could not heat more than three or four at one time, and our constant attention was required during the high frequency treatment. On examination of charts 1 and 2, it will be noted that the growth curves for the two groups (treated and untreated) of rats in

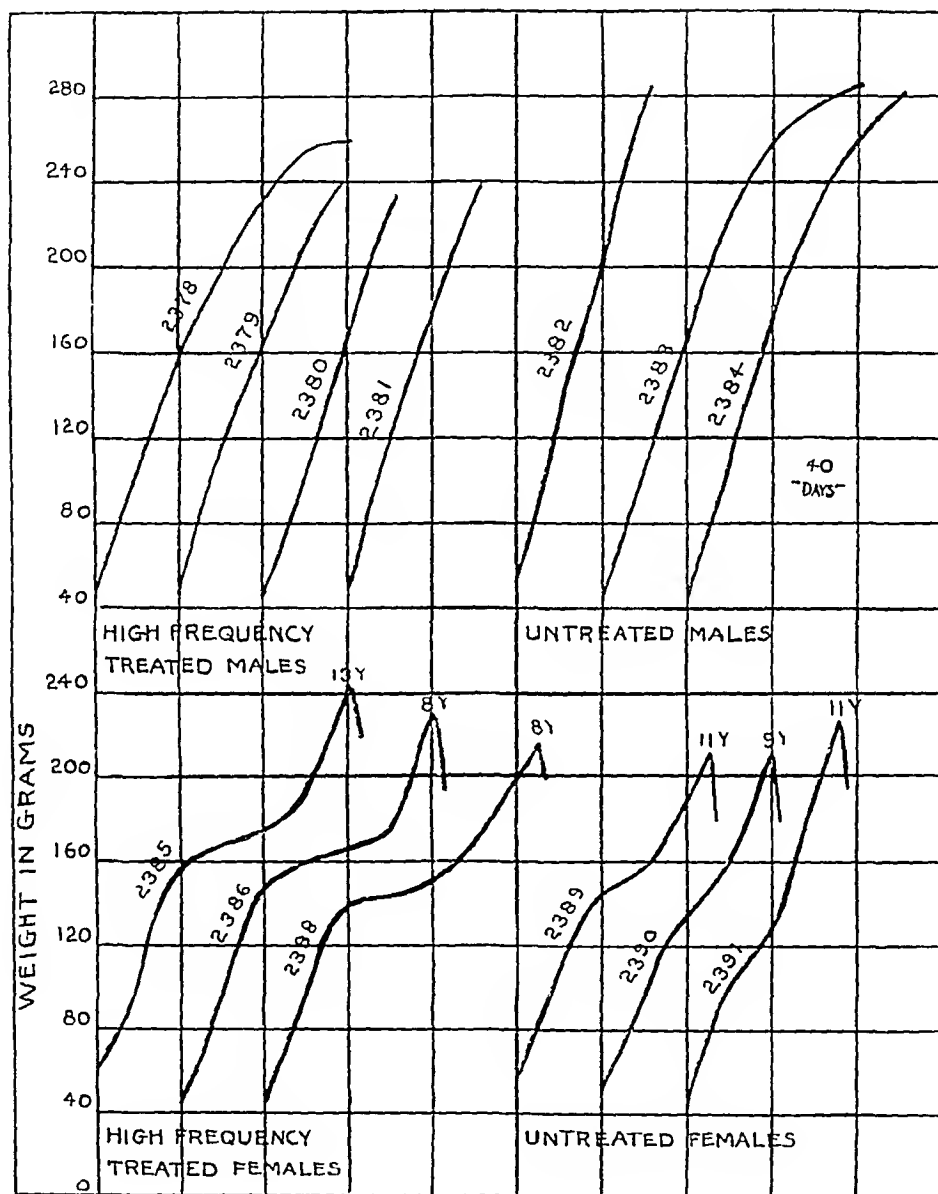


Chart 2—Experiments of the 1930 series showing the effect on growth of exposure of rats to ultrahigh frequency field. Rats in this series were fed on Bills' modification of Steenbock's stock diet.

each series run closely parallel. We might say that the heated rats are just a trifle stunted in their growth, although the number of rats studied are too few to draw this conclusion. In other words, rats can be heated repeatedly to from 39.5 to 40.5 C without any marked interference in

their growth, and it should be emphasized that these experiments are at the period of greatest growth impulse. Another interesting point in regard to these two charts is that the growth curve of the 1930 series is much better than the 1929 series. The growth curve for the 1929 series follows closely that given by Donaldson.⁸ The growth curve for the 1930 series is similar to that reported by Smith and Bing.⁹

The data on reproduction and rearing of the young are also of considerable interest. In the first series of experiments the males and females were not caged separately, and it will be noted from the table that the treated females did not have young until an average period of 120 days of age while the untreated females had young at 95 days of age. There is also a slight difference in the two groups, in the weight of the young at the age of weaning, but the difference is so small and the number of young averaged is not sufficient to draw any definite conclusions.

In the 1930 series, the females were not mated until they were 90 days of age, nevertheless, the treated females did not have young until an average period of thirty days later. Again there is a slight difference in the two groups in the average weight of the young at time of weaning.

A pathologic examination of the tissues of a number of these rats that were treated for a period of three months was made by members of the Department of Pathology.¹⁰ They reported that the treated animals showed little change from the untreated ones. In the males, there was often observed an exhaustion or marked retardation of spermatogenesis with exfoliation of the germinal epithelium and proliferation of Sertoli's cells.

CONCLUSIONS

Exposure of young rats to an ultrahigh frequency field for periods of from one-half to one hour daily and raising their body temperature to 40.5°C does not seem to retard their growth appreciably. The reproductive organs in the male and female rats are not appreciably affected, so that there is no loss in power to breed. Repeated exposure of rats to an ultrahigh frequency field in which the body temperature is raised to 40.5°C does not produce any abnormal pathologic lesions.

⁸ Donaldson, H. H. *The Rat*, ed. 2, Philadelphia, Wistar Institute, 1924, p. 176.

⁹ Smith, A. H., and Bing, F. C. *J. Nutrition* **1**: 179, 1928.

¹⁰ Dr. V. C. Jacobson and Dr. K. Hosoi examined the tissues of these rats.

PHYSIOLOGIC AND BIOCHEMICAL CHANGES RESULTING FROM EXPOSURE TO AN ULTRAHIGH FREQUENCY FIELD^{*}

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The study of the biologic effects on animals of electrical oscillations of very high frequency generated by a vacuum tube oscillator has opened a new field of investigation. During the operation of a short wave radio transmitter, striking heating effects in the vicinity of the antenna were noted¹. Hosmer has shown that there is a well defined relation between the rate of heating of solutions of different salt content and the frequency of voltage alternations. Thus at a frequency of 25,000,000 cycles (12 meters wave length), a 0.05 per cent solution of sodium chloride heats fastest, while at a frequency of 10,000,000 cycles a 0.025 per cent solution heats fastest. Solutions of different salts but of the same electrical conductivity, heat alike. The heating effect is developed within the solution itself. The plates remain cold at all times and are separated by an air gap from the introduced container and other objects under study. Contact with plates will produce arcs and burning and charring of inflammable materials which touch them.

The first scientific investigation of the effect of these oscillating fields on living cells was reported by Gosset, Gutmann, Lakhowsky and Magrou in 1924². They showed that plant tumors exposed to the radiation from a vacuum tube oscillating at 150,000,000 cycles per second (2 meters wave length) were destroyed. Schereschewsky³

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¹ A preliminary report of this paper, under the title "Chemical Changes in the Body Resulting from Exposure to Ultra High Frequency Field. I. Blood Chemical Findings in the Dog. II. Acid-Base Balance in the Plasma of Dogs," was given at the Thirteenth International Physiological Congress, held at Boston, August 1929.

¹ Hosmer, H. R. Science **68** 325, 1928

² Gosset, A., Gutmann, A., Lakhowsky, G., and Magrou, J. Compt rend Soc biol **91** 626, 1924

³ Schereschewsky, J. W. Pub Health Rep **41** 1939, 1926

studied the effect of these radiations on mice. With frequencies varying from 8,300,000 to 135,000,000 cycles per second (equivalent of wave length from 36.1 to 2.2 meters), he observed severe symptoms which may result in death if the exposure is prolonged. Part of the symptoms, at least, he assumed is due to heat retention. He also claimed that the band of frequency between 20,000,000 and 80,000,000 cycles per second (wave lengths from 15 to 3.8 meters) exerts a specific effect on living cells. The rectal temperature of a live mouse could be raised from 5 to 6 C by these currents, while that of a freshly killed mouse could be raised only from 0.1 to 0.7 C in a similar length of time, which was taken to indicate that the heating effect with these currents was different from the diathermic effect observed at lower frequencies. In a subsequent paper,⁴ Schereschewsky proceeded to investigate the effect of these radiations on transplantable tumors and claimed that he has been able to produce complete recession of the tumor and consequent recovery of the tumor-bearing animal.

Christie and Loomis⁵ do not support the theory of Schereschewsky that certain wave lengths have a specific action on living cells. They studied the effect of frequencies ranging from 8,300,000 to 158,000,000 cycles and showed that the lethal nature of these radiations is proportionate to intensity of the field up to a frequency of about 50,000,000 cycles. At frequencies higher than this, the lethality of the radiation appears to diminish. They expressed the belief that the lethal effect of these currents is fully explained on the basis of the heat generated by high frequency currents which are induced in them. In experiments with *Paramecium*, Kahler, Chalkley and Voegtlin⁶ agreed with Christie and Loomis that the effect of a high frequency field depends primarily on the production of a rise in temperature in the organism.

In view of the fact that the general effect on animals when placed in a high frequency field is a marked heat production throughout the body and that the method of heating promises to be of considerable therapeutic value, it was thought that it would be of particular interest to study some of the chemical changes produced in the body.

PHYSICAL APPARATUS

For generating the high frequency oscillatory current, an oscillator designed by the General Electric Company, delivering 150 watts of power at high frequencies of from 9,000 to 12,000 kilocycles was used. The details of the hookup are shown in figure 1, and figure 2 shows the general appearance of the apparatus.

4 Schereschewsky, J. W. Pub. Health Rep. **43** 927 1928.

5 Christie, R. V., and Loomis, A. L. J. Exper. Med. **49** 303 1929.

6 Kahler, H., Chalkley, H. W. and Voegtlin, C. Pub. Health Rep. **44** 339 1929.

as used in our experiments with the crate in position between the condenser plates. The condenser plates are adjustable as to height and spacing. These adjustments allow accommodation for various sizes of materials. Dr W R Whitney of the General Electric Company, placed the apparatus at our disposal, and members of his research staff, particularly A B Page and K C DeWalt, gave technical assistance from time to time.

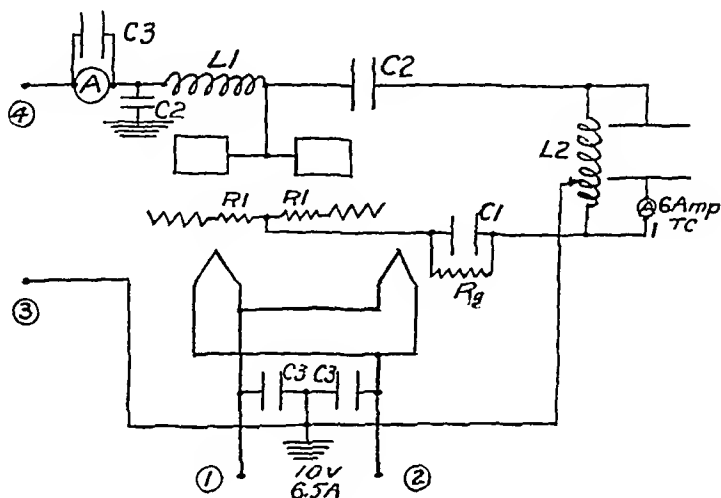


Fig 1—Wiring diagram of a 30 meter oscillator equipped with two UX 852 tubes. *A1* indicates 0-6 amperes full scale deflection thermocouple ammeter, type Do6, *A2*, 0-500 milliamperes full scale deflection ammeter, type Do4, *L1* chock coil, *L2*, 8 turn coil copper wire $\frac{1}{4}$ by $\frac{5}{16}$ inch, *C1*, 0.002 microfarad capacity condenser UC 1014 or 1874K, *C2*, condenser UC 2224, *C3*, Faradon model T condenser, 0.01 microfarad capacity, *Rg*, large blue sticks, resistance 10,000 ohms *R1*, resistance, 10 volts, 6.5 amperes



Fig 2—High frequency oscillator

EXPERIMENTAL WORK

The experiments about to be described were planned to determine the chemical alterations brought about by excessively high temperatures produced by ultrahigh frequency and to determine, if possible, by

chemical methods, temperatures at which it would be safe to heat animals without producing any serious damage

Unfortunately, no laboratory animal which could be strictly comparable to man (except perhaps the horse) seems to be entirely suitable for these experiments. Facilities for handling horses were not available, and dogs were therefore selected as being the best adapted for the work. In these experiments, the changes produced in the blood were studied because of the rapidity and accuracy with which it reflects changes taking place throughout the organism and because of the ease with which it can be sampled at intervals without producing any serious impairment per se.

All the dogs used in these experiments were mongrels varying in weight from 7 to 25 Kg. They were put on Cowgill's⁷ "synthetic" food mixture. During the period of eighteen hours preceding each experiment, no food was given.

The general procedure in our experiments was to bleed the dog from the external jugular vein before and after exposure to high frequency treatment. In collecting the blood great care was taken to avoid any stasis and to collect it under oil. The blood was allowed to clot and then centrifugated. Determinations were then carried out on the serum. In a few experiments determinations were made on the whole blood. The dog was then placed in a wooden crate of suitable size and placed between the plates of the condenser. In some cases the exposures were made for only short periods of thirty minutes, and in other cases they varied from thirty minutes up to as long as twelve hours. The rate of heating of the animal is dependent to a certain extent on the distance between the plates and on how much of the area between the plates is filled up by the animal. Several experiments have been carried out in which the dog was heated rapidly within half an hour to temperatures of from 42.5 to 43 C. In other experiments, the dogs were brought up to a certain temperature in from thirty to sixty minutes, and attempts were made to keep them at that temperature for varying periods of time. It would have been desirable in all these experiments to have control over the temperature and humidity of the room during the treatment, but this was not possible.

The volume of blood was determined by the blood volume method of Hooper, Smith, Belt and Whipple,⁸ brilliant vital red being used. Cell volumes were determined in duplicate with the Van Allen⁹ hematocrit, 16 per cent sodium oxalate solution as diluent being used. The improved Newcomer¹⁰ method was used in the estimation of hemoglobin. For p_H , the quinhydrone procedure of Cullen¹¹ was used on serum. The p_H values were determined at room temperature and calculated to 38 C (using the calculation $p_{Ht} = p_H - (0.01 \times [t' - t])$). Carbon dioxide was determined by the Van Slyke and Neill¹² manometric

7 Cowgill, G. R. J. Biol. Chem. **56** 725, 1923

8 Hooper, C. W., Smith, H. P., Belt, A. C., and Whipple, G. H. Am. J. Physiol. **51** 205, 1920

9 Van Allen, C. W. J. Lab. & Clin. Med. **10** 1027, 1925

10 Newcomer, H. S. Biol. Chem. **37** 465, 1919, **55** 569, 1923

11 Cullen, G. E., and Beilmann, E. J. Biol. Chem. **64** 727, 1925. Cullen, G. E., and Earle, I. P. J. Biol. Chem. **61** 523, 1928

12 Van Slyke, D. D., and Neill, J. M. J. Biol. Chem. **61** 523, 1924

TABLE 1.—Data on High Frequency Treatment of Dogs

Date, 1929	Dog	Total Exposure, Hours	Rectal Temperature, C		Average Temperature, C	Maintained, Hours	Cell Volume, per Cent	pH (38 C)	Inorganic Phosphorus, Milliequivalents	Total Protein, Milliequivalents	Bicarbonate, Milliequivalents	Chloride, Milliequivalents	Lactic Acid, Milliequivalents	Total Base, Milliequivalents	Nonprotein Nitrogen, Mgr per 100 Cc	Sugar, Mgr per 100 Cc	Calcium, Mgr per 100 Cc	Red Blood Cells, Millions	White Blood Cells, Thousands	Differential White Count					Comment
			Before and After	Maximum																Neutrophils	Eosinophils	Monocytes	Lymphocytes		
1/1	*25	0	38.0	38.0	38.0	4	43.0	7.30	2.60	33.8	8.7	87.2	5.5	126	27.9	86	10.1	8.4	10.1	38	40	7.0	6.0	Lymphocytes	
1/4	*25	0	38.9	38.0	38.0	4	43.0	7.37	2.44	40.9	8.2	90.6	3.3	151	29.7	66	9.7	8.18	14.4	10	3.0	2.0	2.0		
1/5	23	0	38.0	38.0	38.0	3	43.0	7.38	2.35	35.9	5.5	90.6	6.2	126	45.1	104	10.9	7.52	10.9	93.0	7.0	5.0	5.0		
1/8	23	0	38.0	38.0	38.0	3	43.0	7.36	2.19	37.5	5.5	87.5	3.9	108	45.1	100	8.9	6.63	9.2	88.0	12.0	6.0	6.0	1½ hours after treatment, 3 days later	
1/8	23	0	39.2	42.2	41.2	5	49.0	7.63	2.78	30.8	17.7	83.8	10.8	136	44.5	149	15.3	8.14	20.3	67.0	10.0	1.0	1.5	Died 1½ hours after treatment	
1/15	24	3	42.9	43.3	42.3	7½	54.0	7.14	3.32	26.0	11.1	117.0	9.3	117	58.8	151	11.4	8.36	10.4	79.0	0.5	4.5	7.0	Died 30 minutes after treatment, 20 nucleated reds to 200	
1/25	25	0	39.0	41.7	41.1	3	36.0	7.23	4.37	12.6	14.6	120.0	148	26.6	134	12.2	6.11	9.7	59.0	5.0	3.5	32.5	3.5		
1/25	25	0	39.1	41.7	41.1	3	32.0	7.23	4.18	13.1	14.2	115.0	162	33.8	134	11.1	7.01	21.8	7.3	53.0	3.0	8.0	36.0	11.0	
1/5	25	4½	41.9	42.5	41.1	3	37.5	7.23	3.75	15.8	12.7	137.0	203	37.0	145	10.8	6.09	12.1	82.0	1.0	7.0	9.0	22.5	7.0	
1/5	25	4	43.3	43.3	41.8	4	46.0	7.25	2.54	19.0	11.1	131.0	5.5	170	30.9	86	12.9	6.57	26.0	80.0	1.5	1.5	19.5	1.5	
1/8	25	0	38.4	43.4	41.8	4	44.0	7.32	4.36	15.1	17.0	113.0	3.9	176	57.6	121	11.5	5.28	9.8	57.0	3.0	6.0	31.0	3.0	
1/8	25	0	39.6	43.6	41.7	3	28.0	7.32	3.90	11.7	18.0	108.0	2.8	163	30.0	121	12.6	4.42	11.0	75.0	0.5	3.0	21.5	3½ hours in crate without treatment	
1/12	25	0	39.2	43.9	41.3	24.0	24.0	7.39	4.13	12.7	18.0	113.0	3.1	160	20.0	120	13.5	4.42	11.0	75.0	0.5	3.0	21.5	2 hours later	
1/12	25	4	39.1	42.8	41.9	7½	27.0	7.26	4.33	16.0	15.6	112.0	175	32.8	148	10.6	4.66	10.8	70.0	11.0	11.0	19.0	3.0		
7/8	25	2	42.5	43.5	43.5		46.0	7.28	4.00	13.7	11.4	129.0	6.2	153	30.8	120	15.3	5.88	28.8	87.0	3.0	2.0	66.0	3.0	
1/1	26	0	40.0	43.4	41.9	2	49.0	7.45	4.35	17.2	22.1	119.0	12.6	200	27.5	101	10.7	4.66	57.8	57.0	3.0	4.0	46.0	3.0	
1/1	26	2	43.4	44.4	42.9	2	53.0	7.63	2.54	20.2	11.6	126.0	20.0	202	28.1	79	11.9	8.61	10.5	73.0	3.0	3.0	36.0	3.0	
1/22	27	0	39.4	43.4	42.2	2	45.0	7.29	2.95	17.0	16.0	118.0	16.1	161	42.2	131	7.46	19.6	80.0	1.0	8.0	5.0	4.0	5.0	
1/22	27	2	43.4	44.4	42.2	2	46.0	7.21	3.19	30.2	4.38	12.0	17.4	174	33.8	185	8.76	15.4	90.0	1.0	3.0	4.0	4.0	4.0	

method Base present as bicarbonate was calculated in millimols by use of the following equation¹³ where carbon dioxide represents the per cent by volume of carbon dioxide content

$$B_{HCO_3} = \frac{CO_2 - \left(\frac{14.04}{\text{antilog}(pH - 6.1)} \times 0.713 \right)}{2.24}$$

Nonprotein nitrogen and sugar were estimated by the Folin-Wu¹⁴ procedure. Inorganic phosphates were determined by the method of Fiske and Subbarow¹⁵ and calculated to milliequivalents of phosphorus per liter by multiplying the milligrams per hundred cubic centimeters by the factor $\frac{18}{31.04}$. Clark and Collip's¹⁶ modification of the Kramer-Tisdall method was used for calcium. Lactic acid was estimated by the method of Friedemann, Cotonio and Shaffer,¹⁷ the condenser unit of Davenport and Cotonio¹⁸ being used. By dividing the milligrams per hundred cubic centimeters by 9, the lactic acid was converted to milliequivalents.

For total base the micromethod of Stadie and Ross¹⁹ was used. Chlorides were determined by the Whitehorn²⁰ method and were calculated to milliequivalents by dividing the milligrams per hundred cubic centimeters by 5.85. Total blood proteins were determined by a micro-Kjeldahl method with direct nesslerization. The more recent equation of Van Slyke and associates²¹ for the base combining power of the total protein of serums were used. Assuming a ratio of albumin:globulin as 1.8:1, it is $B_p = 1.072 P_T (pH - 5.04)$.²²

RESULTS AND COMMENTS

The total number of experiments that were carried out together with the experimental data obtained are indicated in table 1.

Effect of High Frequency Heating on the Animal—Animals placed in the high frequency field showed considerable variation in their response to any given quantity of current, some being more restive than others. That the humidity and the temperature of the room had an effect was noticeable from the fact that on warm humid days in the summer, animals were found to heat up much more rapidly. The heating effect was felt almost as soon as the current was turned on and dogs

13 Peters, J. P., Bulgei, H. A., Eiseman, A. J., and Lee, C. *J. Biol. Chem.* **67**: 141, 1926.

14 Folin, O., and Wu, H. *J. Biol. Chem.* **38**: 81, 1919.

15 Fiske, C., and Subbarow, Y. *J. Biol. Chem.* **66**: 375, 1925.

16 Clark, E. P., and Collip, J. B. *J. Biol. Chem.* **63**: 461, 1925.

17 Friedemann, T. E., Cotonio, M., and Shaffer, P. A. *J. Biol. Chem.* **73**: 335, 1927.

18 Davenport, H. A., and Cotonio, M. *J. Biol. Chem.* **73**: 359, 1927.

19 Stadie, W. C., and Ross, E. G. *J. Biol. Chem.* **65**: 735, 1925.

20 Whitehorn, J. C. *J. Biol. Chem.* **65**: 449, 1925.

21 Van Slyke, D. D., Hastings, A. B., Miller, A., and Sendroy, J. *J. Biol. Chem.* **79**: 769, 1928.

22 Peters, J. P., Wakeman, A. M., Eiseman, A. J., and Lee, C. *J. Clin. Investigation* **6**: 517, 1929.

would usually begin to pant within two or three minutes after starting the experiment. In general, it was noticed that animals were more irritable while their temperature was being raised, maintenance or reduction of temperature from higher levels did not materially affect the animal. The respiratory movements in most cases became extremely rapid and were maintained at a high rate for varying periods after the treatment. In some of the longer experiments in which the temperatures were above 42.6 C and death the usual result, it was noticed that after the very rapid respiration it became shallow and weak, and finally the animal died of respiratory failure. The dogs heated to high temperatures frequently developed diarrhea and in some instances abdominal cramps were noticeable. There was always evidence of intense fatigue.

Some of the dogs made efforts to escape from the crate while others were quite placid. It was observed that animals reacted to increased current by increase in the rate of rise in temperature up to a certain point, about 42 C. At this point, the organism showed a definite resistance to increased temperature. Finally, the mechanism for the elimination of heat would break down, after which an increase in the rate of temperature rise would occur. Great care is necessary when heating above this critical point. Flinn and Scott²³ and Henderson and Haggard²⁴ have noted similar physiologic limitations. A reflection of this great resistance to change in temperature at this critical point is seen in the values for the carbon dioxide content.

In the production of artificial fever by this method, it is of interest to know how long the fever is maintained. When animals were heated to a temperature of from 41 to 42 C, it was noticed that return to normal temperature occurred within about thirty minutes. With higher temperature, from 42 to 43 C, the return to normal was usually slower, varying from sixty minutes to two hours. In a few instances with the higher temperature, the animals either died shortly after treatment or did not return to normal temperature and died within a few hours of treatment.

The pathologic changes produced in the tissues of these heated animals is discussed in detail in a paper by Jacobson and Hosoi.²⁵

Effect of High Frequency Treatment On the Blood Volume, Cell Volume, Hemoglobin and Weight—In the consideration of the effect of high frequency treatment, it is necessary to consider not only the total period of heating and the average or maximum temperature but also the rate of heating. Table 2 gives results of several experiments in which

23 Flinn, F. B., and Scott, E. L. *Am J Physiol* **66** 191, 1923.

24 Henderson, Y., and Haggard, H. W. *J Biol Chem* **33** 333, 1918.

25 Jacobsen, V. C., and Hosoi, K. *The Morphologic Changes in Animal Tissue Due to Heating by an Ultrahigh Frequency Oscillator*, this issue, p. 744.

the animals were heated to various average temperatures for different periods of time. It is seen that in those animals which were not allowed water during the treatment that the percentage of loss in weight varies with the length and intensity of treatment, the loss in weight in some of the experiments amounting to as high as from 10 to 11 per cent. The loss in weight is undoubtedly due largely to loss of water through the lungs by hyperventilation. Whenever the animals were given water to drink the percentage of loss in weight was greatly reduced. The animals usually regained their original weight in twenty-four hours.

TABLE 2—*Effect of High Frequency Treatment on Blood Volume, Cell Volume, Hemoglobin and Weight*

Date, 1929	Dog	Total exposure, Hours	Maximum Rectal Temperature, C	Weight			Blood Volume			Cell Volume			Hemoglobin		
				Before, kg	After, kg	Loss, per Cent	Before, Cc	After, Cc	Decrease, per Cent	Before, per Cent	After, per Cent	Change, per Cent	Before, per Cent	After, per Cent	Change, per Cent
3/1	23*	4½	40.0	15.10			1,680	1,400	16.5	38.0	43.0	+13.0			
3/4	23*	5½	41.5	14.88	13.71	7.9				38.0	43.0	+13.0			
3/15	24*	3	43.3	9.58	8.87	7.4	681	423	24.9	43.0	54.0	+25.6			
3/25	25*	4½	41.7	10.48	9.74	6.9				36.0	36.0	0			
3/29	25*	4¾	42.5	10.48	9.45	9.8				32.0	37.5	+17.0			
4/5	25*	4	43.0	10.78	9.75	9.6	919	694	24.5	38.5	46.0	+19.5			
4/12	25*	4	42.8	10.97	9.97	10.0									
4/26	28*	5¼	41.7	9.05	8.04	11.1				42.0	57.0	+35.0	12.35	19.06	+62.0
5/1	28*	3½	42.2	8.20	7.81	4.8									
5/20	29*	½	41.4	15.00	14.65	2.3				40.8	41.0	+0.5	14.03	14.38	+2.5
5/24	29*	½	41.5	15.70	15.40	1.9	1,235	1,110	9.9	40.6	43.3	+6.6	14.26	14.57	+4.3
6/4	30†	4½	41.6	7.90	7.65	3.2									
6/6	34†	12	43.1	13.70	13.40	2.2	1,250	1,055	21.8	41.0	56.0	+21.0	13.29	20.60	+55.0
6/17	33†	6	42.3	10.20	9.48	7.0							13.40	14.50	+12.0
6/20	35†	5	42.3	10.10	9.70	4.0				34.0	53.5	+57.0	12.18	14.61	+20.0
6/27	32†	5	42.1	14.70	14.48	2.2	1,162	1,012	12.9	38.5	42.5	+10.4	12.99	14.26	+10.5
7/1	32†	5	42.1	14.30	13.77	3.6				34.5	34.5	0	12.44	12.62	+1.4
7/2	36†	6	40.8	13.77	13.44	2.4	945	908	3.9	38.0	40.0	+5.2	14.61	15.53	+6.3
7/8	25†	2	43.7	15.30	14.88	2.7				46.0	53.0	+15.2	16.7	17.53	+5.0
7/11	36†	5¼	41.1	13.20	12.94	2.0	970	870	10.3	33.0	40.0	+21.2			
7/15	36†	5¾	42.0	12.70	12.30	3.2	869	783	9.9	37.0	43.5	+17.5	12.99	13.81	+6.3
7/19	36†	5½	41.7	12.30	12.00	2.3				35.0	38.5	+10.0	11.39	11.69	+2.6

* No water during treatment

† Water during treatment

This excessive loss in water is apparently responsible for the decrease of blood volume. In all of our experiments in which the blood volume was measured, there was a decrease in volume varying from 3 to 25 per cent. The concentration of the blood is also evidenced by the increase in cell volume and hemoglobin, which runs somewhat parallel with the decrease in blood volume. These results are in line with those of Flinn and Scott,²³ who found that there was blood concentration in dogs on exposure to extreme heat. At high temperature, the rate of replacement of water cannot keep pace with the rate of the loss, and a certain amount of concentration results. The concentration of blood can apparently be reduced as much as 25 per cent with recovery of the animal to normal condition.

Effect of High Frequency Treatment on the Acid Base Equilibrium of the Blood—In order to obtain a better idea of the changes brought about by high frequency heating, a tabulated summary of most of the experiments listed in table 1 has been prepared. First of all we have taken the values obtained before treatment on twenty-four experiments and determined the averaged values. The experiments were divided into two main groups, those heated for one-half hour and those heated from two to six hours. In the short periods there is one series of three experiments in which dogs were heated to a maximum rectal temperature of 41.7 C and in a second series of two experiments they were heated to 43.2 and 46 C respectively. Both of these dogs died within fifteen minutes after the treatment. In the longer periods of treatment we divided the experiments into three series. In the first series there are seven experiments in which the maximum temperature was between 41.1 and 41.7 C, another series of six experiments in which the temperature was brought up to from 42.2 to 42.8 C and a third series of six experiments with a maximum temperature of 43.3-44 +C. In this third series only one of the six dogs recovered after the treatment the remainder died within an hour. The averaged values for each of these series of experiments are given in table 3.

The rise in temperature of the animal causes a marked hyperpnea, and as a result there is a great washing out of carbon dioxide and the bicarbonate content of the blood is consequently reduced. This reduction of bicarbonate bears a direct relation to the rate of heating and temperature attained. It is most marked in the short rapid period of heating with high temperature of from 43 to 44 C in which series of experiments the bicarbonate was reduced to the low level of 7 millimols. According to Haggard,²⁶ Koehler,²⁷ and others,⁻⁸ such changes with hyperpnea in man result in an increase in p_{H} . Flinn and Scott²⁸ have also noted that exposure of dogs to environmental temperature above 40 C results in a marked increase of p_{H} .

In none of our experiments was a distinct alkalosis noted, although a tendency in that direction is indicated in the three experiments of one-half hour treatment with a maximum temperature of 41.7 C. In this series of experiments, the p_{H} showed an average increase of 0.07. It may be that a greater alkalosis was not indicated due to the production of lactic acid which is almost doubled in this series over the values before

²⁶ Haggard, H. W. J. Biol. Chem. **44** 131, 1920.

²⁷ Koehler, A. E. Arch. Int. Med. **31** 590, 1923.

²⁸ Cajori, J. A., Crouter, C. Y., and Pemberton, R. J. Biol. Chem. **57** 217, 1923.

heating In the two experiments in which the animals were brought up to a temperature of 43.2 C and 46 C within half an hour, the p_H was greatly reduced, indicating a marked acidosis. The average p_H for this series was 6.89, which is on the acid side of neutrality. This marked acidosis would be sufficient to account for the death of these animals. It is also of interest to note that the lactic acid is increased in these experiments to more than five times the values before treatment. These observations are comparable with those of Austin, Sunderman, and Camack²⁹ on cold-blooded animals. They observed that with an increase of from 15 to 20 C change in the environment of alligators, there results a lowering of p_H and formation of considerable amounts of lactic acid.

TABLE 3—*Tabulated Summary of High Frequency Experiments on Dogs, Averaged Values*

High Frequency Exposure	Number of Experiments Averaged	Maximum Temperature, C	p_H at 38 C	Inorganic Phosphorus, Milliequivalent	Total Proteins, Milliequivalent	Sodium Bicarbonate, Milliequivalent	Chloride, Milliequivalent	Lactic Acid, Milliequivalent	Total Acid, Milliequivalent Columns 1+5+6+7+8	Total Base, Milliequivalent	Nonprotein Nitrogen Mg per 100 Cc	Sugar, Mg per 100 Cc	Calcium, Mg per 100 Cc
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)
Before treatment	25	39.0*	7.30	3.04	14.8	16.4	110	4.6†	149	153	30.8	120	11.9
½ hr treatment	3	41.7	7.57	1.74	16.3	17.3	109	9.3	150	151	33.7	171	11.6
½ hr treatment	2	43.3‡	6.89	3.07	16.0	7.0	110	24.6	161	133	52.9	256	11.5
4.6 hrs treatment	7	41.1-41.7	7.31	1.89	14.9	13.8	118	5.8	154	155	28.9	125	11.8
4.6 hrs treatment	6	42.2-42.8	7.21	3.49	13.7	11.9	113	9.2‡	151	162	64.4	154	11.9
2 ½ hrs treatment	6	43.3-44+	7.24	2.92	20.1	10.3	120	14.4	168	175	61.2	125	11.7

* Average temperature before treatment

† Average of thirteen normals

‡ Average of two experiments only

In these short rapid periods of heating, the animal has no chance to compensate appreciably for the changes brought about, and the effects of temperature per se on biologic functions are observed.

The longer periods of heating do not show any striking changes in p_H although with dogs heated above 42 C there is a tendency toward acidosis. The lactic acid is also greatly increased in these series of experiments. The increase in lactic acid is probably due to the fact that as a result of a rise in temperature, metabolism is greatly increased resulting in a tissue anoxemia. Also it may be that lactic acid is augmented to some extent by the increased muscular activity in those dogs which resisted treatment.

The chloride is not significantly affected by the high frequency treatment. In a few experiments the chloride is increased from 10 to 15 per cent but these changes can be accounted for by the blood concentration. In the averaged values in table 3, the only significant change in chloride is in the last series of experiments in which the animals were heated from 43 to 44 C for periods of from two to four hours.

The total proteins tend to be slightly increased in the majority of experiments. This may be the result of blood concentration, and undoubtedly is the explanation for the marked increase in the last series of experiments with temperatures of from 43 to 44 C.

The changes in inorganic phosphorus in the blood were somewhat variable. In the short and long periods of treatment with maximum temperature of 41.7 C, there is a marked reduction of from 25 to 35 per cent for the averaged values. With the higher temperatures, the averaged values are not significantly changed. It is difficult to associate the changes in inorganic phosphorus in these experiments with any definite mechanism.

The total base content of the serum does not seem to be particularly affected except in the long periods with temperatures above 42 C, in which experiments there is a small increase. These changes can be accounted for by the dehydration with subsequent concentration of the blood. The calcium is not appreciably altered as is indicated by averaged values for this series of experiments.

Effect of High Frequency Heating on the Nitrogenous Constituents and Sugar of the Blood — The general effect of high frequency heating is to bring about an increase in nonprotein nitrogen in the blood. In the short period of heating with a maximum temperature of 41.7 C, it will be noted from table 3 that there is an increase of about 10 per cent in nonprotein nitrogen, while with the higher temperature of 43.3 C, the averaged value shows an increase of 75 per cent. In the longer periods of treatment, the nonprotein nitrogen is still further increased. The averaged values for temperatures above 42 C show an increase over 100 per cent, and in several experiments the increase is over 200 per cent. An exception to this increase in nonprotein nitrogen seems to occur in the series of experiments in which the animals were treated from four to six hours and brought up to a temperature of from 41.1 to 41.6 C. However, the nonprotein nitrogen of the series before treatment is lower than the average for the whole series, and there is an increase for this series from 23 mg before treatment to 28.9 mg after treatment, or about 25 per cent.

Blood concentration may account for part of the increase in nonprotein nitrogen, but in many of the experiments the increase in nonpro-

tein nitrogen is all out of proportion to the blood concentration. Other contributing factors to this increase would be the increase of metabolism resulting from the rise in temperature. As pointed out by Du Bois,³⁰ metabolism follows the temperature law of Van't Hoff, which would mean that for every rise of 10 C the rate of oxidation would be increased 2.5 times. With the rise in temperature an oliguria occurs and the production of metabolites, which continues whether urine is excreted or not, results in an accumulation in excess in the body.

Several experiments have been carried out in which the urea, creatinine and amino-acid nitrogen have been determined to see whether any particular nitrogen component is responsible for this increase of

TABLE 4—*Effect of High Frequency Treatment on the Nitrogenous Constituents of the Blood*

Date, 1929	Dog	Total Expo- sure, Hours	Rectal Temperature, C		pH (38 C)	Non protein Nitrogen, Mg per 100 Ce	Urea Nitrogen, Mg per 100 Ce	Creat inine, Mg per 100 Ce	Amino Acid Nitrogen, Mg per 100 Ce
			Before and After Exposure	Maxi- mum					
7/29	38	0	39.0		7.31	46.5		1.2	6.5
		1¾	43.6	43.6	7.16	158.0		1.3	13.5
7/30	39	0	39.1		7.33	30.3	20.8	1.8	5.2
		1½	43.6	43.6	7.15	88.0	48.4	2.3	12.4
7/31	40	0	38.7		7.41	19.7	14.7	1.1	7.7
		2½	43.3	43.3	7.35	42.9	30.2	1.7	8.5
8/ 2	37	0	39.3		7.41	24.9	17.1	1.5	7.6
		2¾	43.6	43.6	7.26	55.5	31.2	1.9	12.4
1930									
1/24	42	0	39.4			37.0	12.5	1.1	7.3
		3¼	40.6	40.8		48.8	23.6	1.3	7.2
1/28	42	0	39.4			42.0		1.6	7.9
		3	40.5	41.4		51.2		1.8	8.6
1/30	42	0	39.5			33.0	14.8	1.2	
			40.2	40.5		46.5	31.0	1.2	

nonprotein nitrogen. These experiments are listed in table 4. It will be noted that urea, creatinine and amino-acid nitrogen are increased along with the increase in nonprotein nitrogen. The urea nitrogen is increased somewhat parallel with the nonprotein nitrogen. In the more drastic heatings, the amino-acid nitrogen is increased along with the urea nitrogen and nonprotein nitrogen, while in the experiments with moderate heating the amino-acid nitrogen does not show much change. Creatinine is also increased in some of these experiments, although not in proportion to the other nitrogenous constituents. These experiments would indicate that the increase in nonprotein nitrogen is largely a result of increased metabolism with higher temperature.

The blood sugar content seems capable of considerable variation. We have found instances of considerable increase as well as decrease

30 Du Bois, E. F. Basal Metabolism in Fever, J. A. M. A. 77:352, 1921

on exposure of animals to high frequency heating. In the short periods of heating, the increase in blood sugar is very marked. With a temperature of $43.3 \pm C$ the average increase for the two short period experiments is 113 per cent. Even with a maximum temperature of $41.7 C$, there is an average increase of 42 per cent. In the longer periods of treatment, the averaged values show only a slight increase in the series of experiments with temperatures from 42.2 to $42.8 C$, the average increase for this series of experiments amounts to 28 per cent. In the series with temperatures of from 43.3 to $44.4 C$, the average value shows a slight increase over the normal. However, on examining the individual experiments in this group two of the experiments, those performed on

TABLE 5—*Effect of High Frequency Heating on the Blood Sugar*

Date, 1929	Dog	Total Exposure, Minutes	Rectal Temperature, C	p_H (35 C)	Sugar, Mg per 100 Cc	Nonprotein Nitrogen, Mg per 100 Cc
10/25	41	0	39.4	7.35	118	38.0
		26	41.0	7.35	99	37.0
		50	42.2	7.40	98	
		71	42.0	7.40	110	
		94	41.9	7.10	130	
		116	42.6	7.40	139	
		133	43.5	7.25	264	65.0
11/2	42	0	40.0	7.40	117	53.0
		30	41.1	7.45	129	50.0
		66	41.1	7.45	137	63.0
		102	42.2	7.50	168	75.0
		140	43.0	7.50	196	74.0
11/11	42	0	39.4	7.40	93	43.0
		22	40.5	7.40	112	43.0
		52	41.5	7.40	149	52.0
		82	41.3	7.35	147	54.0
		112	42.2	7.40	157	69.0
		127	43.3	7.20	212	87.0

dog 24, March 15 and on dog 27, April 22, show an increase in blood sugar, while in the other four experiments of this series there is a great decrease in blood sugar. In the experiment of dog 30 June 11, the blood sugar was reduced to the low level of 35 mg.

Three experiments have been carried out in which we have studied the blood sugar concentration at various intervals during the period of treatment. These are listed in table 5. Along with these blood sugar determinations, the p_H and nonprotein nitrogen was also determined. In the first experiment of this series it will be noted that at first there is a temporary drop in blood sugar followed by a rise and the greatest rise seems to occur with the change of p_H toward an acid condition. Within a period of seventeen minutes, the blood sugar rose from 139 to 264 mg. In the third experiment, there is also a great rise in blood sugar with the lowering of p_H . It is rather significant on examination of table 1 that the greatest increases in blood sugar occur in those experiments in

which the p_H has been lowered the most. These increases in blood sugar apparently are due first of all to the increase in metabolism resulting from a rise in body temperature and bringing about a mobilization and breakdown of glycogen. In changing of the blood to a more acid condition the oxidation processes are slowed, resulting in much greater increases in blood sugar.

*Effect of High Frequency Heating on the Numerical and Morphologic Changes in the Blood*³¹—Immediately after heating, there is usually a considerable increase in the number of red blood cells which may vary from 5 to 50 per cent. This is apparently associated with water loss as shown by the loss of weight, the decrease in blood volume, the increase in cell volume and the increase in hemoglobin. It may be in part a primary effect before compensation can take place due to fluid in the tissues becoming available in the circulation. There is, therefore, frequently more change after one or two hours' heating than is found after from four to six hours' heating.

In addition to the increased number of red cells, in many instances there is a marked increase in immature forms of red cells, notably normoblasts and red cells showing polychromatophilia, basic stippling and so-called Howell Jolly bodies. Many investigators³² have noted that the peripheral blood of a large percentage of dogs normally contains nucleated red cells. We³³ have already stated that the changes in the blood of these animals suggested stimulation of the hemopoietic tissue, resulting perhaps from anoxemia, or a mixing of blasts, formerly present, due to a more rapid circulation of blood. Erythropoiesis apparently was accelerated or at least immature red cells were delivered more rapidly to the peripheral blood, as indicated by the increased number of normoblasts polychromatophilic cells and others showing nuclear fragments and basic stippling.

There is also a marked increase in the total white cells due to absolute and relative increase in the polymorphonuclear leukocytes. The lymphocytes and eosinophils are usually relatively markedly decreased. The change in the monocytes is less marked and less constant.

The number of red cells come back to normal more rapidly than do the white cells when the heating is continued for a long period or when the heating has been stopped.

31 The Department of Medicine made the blood counts on most of our experimental animals, and Dr. Thomas Ordway wrote this section on blood.

32 Drinker, C. K., Drinker, K. R., and Kreutzmann, Henry A. J. *Exper. Med.* **27**: 249, 383, 1918.

33 Ordway, Thomas, and Gorham, L. W. *Diseases of the Blood*, Oxford Monographs, New York, Oxford University Press, 1928, vol. 9.

SUMMARY

The body temperature of dogs can be raised to any desired point by exposure to an ultrahigh frequency field. The temperature returns to normal quite rapidly unless the animal has been heated above 42° C. Animals heated above 42.5° C. for any great length of time do not survive treatment, although we have instances of an animal heated momentarily to 44.5° C. surviving.

Exposure of animals to an ultrahigh frequency field results in loss of weight which is dependent somewhat on the length and intensity of treatment. There is also a decrease in blood volume amounting in some experiments to as much as 25 per cent. The concentration of the blood was also evidenced by the increase in cell volume and hemoglobin. Weight and blood volume usually return to normal within twenty-four hours.

Raising the temperature of animals to 41.7° C. does not produce any great change in hydrogen ion content of the plasma although there is a tendency toward a condition of alkalosis. With higher temperatures the tendency is toward a condition of acidosis, apparently caused by great increase in the production of lactic acid. The increase in lactic acid is probably due to greatly increased tissue metabolism resulting in a tissue anoxemia. Changes in the chloride, total protein and total base are accounted for by the dehydration. Bicarbonate was greatly reduced owing to excessive pulmonary ventilation with rise in body temperature. Changes in the inorganic phosphorus were somewhat variable, although with a maximum temperature to 41.7° C. there is a marked reduction.

Nonprotein nitrogen of the blood is generally increased, in some instances the increase is over 200 per cent. Urea nitrogen, creatinine and amino-acid nitrogen are also increased. These increases are accounted for by the increased metabolism resulting from rise in temperature and the oliguria.

The blood sugar content in most of the experiments shows an increase, in some cases amounting to as high as 150 per cent. The greatest increase in blood sugar occurs in those experiments in which the p_H has been lowered the most.

There is an increase in both red blood cells and total white cells. Besides the increase in red cells there is in many instances a marked increase in immature forms of red cells, suggesting a stimulation of the hemopoietic tissues.

THE MORPHOLOGIC CHANGES IN ANIMAL TISSUES DUE TO HEATING BY AN ULTRAHIGH FREQUENCY OSCILLATOR *

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Heat is a manifestation of normal cell metabolism which lends itself readily to measurement, and within the mammalian organism the limits between which cells can maintain life are fairly accurately known. The cell has probably an optimum temperature for the best performance of its duties, its temperature at a given moment being a function of the heat contributed by its neighbors, the degree of radiation from its own surface and the amount of heat generated by the metabolic activity within itself. Extremes of heat and cold are inimical to the normal activity of a cell or cell-composite, and the resultant degeneration or necrosis provides the chemical stimulus for the inflammatory reaction which in the broadest sense begins considerably before the appearance of a cellular exudate.

The body can withstand a much higher temperature than what is regarded as normal, and though a return to normal may follow hyperthermia, and even though a disease may apparently be arrested in its course by an application of heat, it does not alter the fact that many somatic cells have probably been destroyed or pathologically altered by the increased temperature. The more specialized cells of the body are the most sensitive to oxygen want and probably are the more profoundly affected by inflammatory mutants which, of course, include extremes of temperature. Hence in estimating the effects of a given method of applying external heat or of stimulating the internal production of heat a careful experimental study of the functional and morphologic changes in the many types of tissue which make up the body must form the rational basis for any therapeutic applications.

The value of heat in the treatment of disease has been known since the dawn of medical history. The methods of application have been of exceedingly great variety but almost without exception the heat has

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been applied externally, in dry or moist form, the temperature of the internal organs being raised largely by the passage of blood and lymph from the cutaneous field directly exposed to the heat source. The blood and lymph are thus the principal vehicles for the transportation of the heat much as is the fluid in a hot water heating circuit.

Since the therapeutic results of the use of external heat have been well established in a variety of conditions, a device capable of producing hyperthermia by increasing uniformly throughout the body heat production by the cells, would appear to offer a new approach to the experimental study of fever and possibly to increase the scope of therapy based on the febrile phenomenon.

Due to the rapid developments in the field of radio transmission, there has recently been devised in the research laboratory of the General Electric Company under the direction of Dr. W. R. Whitney, a high frequency alternating current heater or oscillator constructed on the principle of a short wave radio transmitter, except that the energy is concentrated between two plate electrodes instead of being directed from an aerial. Previously it had been noticed that when a workman was in the field of a short wave radio transmitter a rise of temperature of as much as 2.2 degrees developed in fifteen minutes, the height of the rise being determined by the time he remained in the field or by his proximity to the apparatus. A detailed description of the machine is to be found in the paper by Knudson and Schaible.¹

A wave length of 25 meters was used in practically all the experiments, at an average of 2,000 volts, amperage from 0.2 to 0.35, oscillating about 10,000,000 per second. A temperature once reached could be maintained either by decreasing the voltage or by increasing the distance between the plate electrodes.

EXPERIMENTAL WORK

The animals used in this investigation were dogs, guinea-pigs and white rats, many given to us by Prof. Arthur Knudson after he had followed the chemical changes of the body fluids. Some animals were from Dr. C. M. Carpenter, who had studied them from a serologic point of view.

Twenty-three dogs were available, eleven of which were males and twelve females. They varied considerably in size and age and most of them were mongrels, three were German shepherd dogs. The breed of dog is probably unimportant although the amount of hairy coat might be worth noting. Four of the twenty-three dogs were long haired. The animals were apparently healthy at the beginning of the experiment.

Eleven dogs were given a single heating, but this involved removing the animal from the machine every thirty minutes to be weighed and to have its temperature taken, from four to seven minutes being required for these procedures. Eight dogs were heated from thirty-seven minutes to two hours and twenty minutes, one dog five and one-half hours, one dog six hours and one dog twelve hours.

¹ Knudson, A., and Schaible, P., this issue, p. 729.

Protocol of Experiments with Dogs

Dog	Breed	Healings	Total Heat	Normal Temperature	Maximum Temperature	Weight Loss, Kg	Manner of Death	Time of Death After Healing	Time, P. M.	Comments
31	Hound	1	37 min	102.7	109.8		Bled	0	0 min	None
26	Terrier	1	1 hr 20 min	104.0	108.5		Bled	5 min	2 hrs	None
39	Police	1	1 hr 30 min	104.7	110.5		Died	6 min	10 min	None
27	Poodle	1	1 hr 36 min	103.0	109.4		Died	20 min	4 hrs 30 min	None
38	Poodle	1	1 hr 40 min	103.0	110.5		Died	30 min	25 min	None
40	Hound	1	1 hr 45 min	101.7	110.0	0.85	Chloroformed	53 hrs	0	None
7	Collie	1	2 hrs 5 min	102.8	111.0		Died	15 min	1 hr	None
41	Spaniel	1	2 hrs 20 min	103.8	110.0		Died	6 min	13 min	None
35	Bull	1	5 hrs 15 min	102.0	108.2		Died	10 min	30 min	None
33	Police	1	6 hrs	102.6	108.0		Died	8 hrs	0 hrs 30 min	None
34	Police	1	12 hrs	102.0	109.6		Chloroformed	6 days	0	None
29	Bull	3	4 hrs 50 min	101.3	111.0		Died	14 min	40 min	Skin burn
37	Mongrel	2	8 hrs 30 min	102.8	110.6	0.1	Died	1 min	35 min	Diaphragmatic hernia
30	Hound	3	8 hrs 40 min	102.1	109.0	0.1	Died	10 min	1 hr	Skin burn
21	Mongrel	3	8 hrs 50 min	101.6	108.7		Died	2 hrs	1 hr 10 min	Skin ulcers
32	Police	2	10 hrs	102.3	108.0	0.25	Chloroformed	8 days	1 hr 30 min	None
28	Terrier	4	12 hrs 23 min	103.0	112.0	1.1	Died	1 min	0	Skin burn
39	Spaniel	3	12 hrs 40 min	101.8	112.4	0.3	Died	0	15 min	Neck abscess
23	Mongrel	9	15 hrs	101.5	108.1		Died	15 min	0	None
43	Hound	9	18 hrs	102.2	108.0	0.4	Chloroformed	5 days	0	None
25	Collie	5	19 hrs	102.3	110.6	0.1	Died	30 min	1 hr	Anemia, skin burns
36	Bull	5	19 hrs 30 min	102.0	108.0	2.0	Died	6 min	9 min	Skin burns
44	Airedale	9	20 hrs 20 min	102.4	107.5	0.4	Chloroformed	1 hr	0	Skin ulcer

The tissues were fixed in Zenker's fluid, 10 per cent neutral formaldehyde and absolute alcohol saturated with mercuric chloride for glycogen

Eight dogs were given single heatings from thirty-seven minutes to two hours and twenty minutes. The maximum temperatures attained were nearly the same in all animals—the lowest 108.3 F, the highest 111 F. The lowest preheating temperature was 101.7 F, in dog 40 which was heated to 110 F, and the highest 104.7 F, in dog 39 whose temperature rose to 110.5 F.

The gross changes observed were few, congestion and edema being the most conspicuous. Rarely cloudy swelling of liver and kidneys was sufficiently marked to be seen with the naked eye. The microscopic alterations will be presented organ by organ.

The heart in five dogs showed acute congestion. Two, which did not show this change, died about the same time after the last heating as those which did. The third dog which showed no congestion died fifty-eight hours after the last heating, in ample time for the tissues to return to normal. Of these five dogs, two showed interstitial edema. Foci of hemorrhage were present in three dogs, one of them, dog 40, was killed with chloroform fifty-eight hours after the last heating. Dog 41, which died six minutes after heating, showed numerous glycogen granules in the muscle fibers. Fat droplets were demonstrated by schiach in dogs 38 and 40, a much greater amount in dog 38, which died ten minutes after heating, and in dog 40, killed fifty-eight hours afterward.

In six dogs there was acute congestion of the lungs but only one with alveolar edema. Emphysema was noted in four dogs. Three of these four also showed areas of atelectasis. Alveolar hemorrhage was found in dogs 39 and 41, hypersecretion of bronchial mucus in dog 31, and vacuolation of bronchial epithelium in 40.

In five dogs the spleen showed acute congestion and foci of hemorrhage in the pulp. In dogs 38, 39 and 41, there was necrosis of the lymphoid centers. Hemosiderin granules were present in dogs 26 and 31, and marked endothelial proliferation of the sinusoids in dogs 31 and 41. Dog 41 also showed diffuse fibrosis and adhesive perisplenitis.

None of this group showed congestion of the gastro-intestinal tract. Dog 26 showed a few mucosal hemorrhages in the ileum, dog 39, necrosis of the lymphoid centers in the ileum and hemorrhage in its mesentery, and dog 31, an excess of mucus in the stomach and colon.

Acute congestion of the liver was seen in all except dog 38, foci of hemorrhage in dogs 39 and 41, and focal necrosis in dogs 26, 38 and 39. Only in dog 40 was there definite cloudy swelling. Glycogen was present in dogs 30 and 41. Much fat was seen in dogs 34, 40 and 27, and was most abundant in the peripheral zones. The other dogs showed smaller amounts of fat.

The only noteworthy change in the pancreas was acute congestion. In dog 38, a lymph node attached showed germinal center necrosis and hemosiderin granules in the sinuses.

The kidneys were rather uniformly congested. There was cloudy swelling in six dogs and hydrops in four. Fat was present in most animals, the greatest amount in dog 38. Dogs 38 and 39 showed an old cortical scar. Glycogen was present in dogs 41 and 36.

The adrenals showed hemorrhages into the overlying fat in dogs 31, 39 and 40, congestion in dogs 38 and 39, increased fat droplets in dog 40, and focal hemorrhages and cortical degeneration in dogs 36 and 41.

There was congestion of the ovary in dog 31, otherwise it was normal.

The testes were normal except in dog 41, which showed exfoliation of the germinal epithelium and giant cells in the lumen of the tubules

Dog 36 had a papillary adenocarcinoma of the breast, which showed nothing striking

Some fatty infiltration and hydrops of the striated muscle were noted in dog 35, and glycogen in dogs 41 and 36

The bone-marrow was active in all

The thyroid was normal except in dogs 38 and 39, which had interstitial hemorrhages. There was no evidence of epithelial hyperplasia

The salivary glands showed congestion

There was congestion of the brain in all the dogs. Meningeal hemorrhages were seen in dog 26, chronic meningo-encephalitis in dog 40, focal hemorrhages in dog 38, and chromatolysis of the ganglion cells in dog 40

In the cord chromatolysis of the anterior horn ganglion cells was noted in dog 40. This may have been a postmortem change

Three dogs were given a single heating of over twice the duration of the former group: dog 35, five hours and fifteen minutes, dog 33, six hours, and dog 34, twelve hours. The normal and maximum temperatures for these animals were practically the same: 108.2, 108 and 109.6 F, respectively. Dog 35 died forty minutes after heating, dog 33 eight hours and dog 34 was killed with chloroform six days later. Dog 34 sustained several skin burns, which did not heal and became superficially infected

There were no gross lesions in the organs of these dogs except congestion of the viscera

Microscopically, the heart was congested, and in dog 35 there were focal hemorrhages deep in the myocardium. Scattered hyaline fibers were seen in dog 33, and in dog 34 there were foci of necrosis. No fat was present

The lungs were congested and showed also small areas of atelectasis and emphysema but no edema. Dog 34 had patches of bronchopneumonia and some alveolar hemorrhage

There was focal hemorrhage and necrosis of the lymphoid centers of the spleen in dogs 33 and 35, the latter showed marked endothelial proliferation

Edema of the wall of the stomach was noted in dog 33. Congestion of the entire gastro-intestinal tract was seen in dog 35 with necrosis in the lymphoid tissue. Loss of Nissl's granules was noted in the ganglion cells of the intestine in dogs 33 and 35

The liver was congested in all three dogs. Focal and central necrosis was noted in dog 33, and marked fatty infiltration in dog 35 with cloudy swelling

In all three animals the kidneys showed congestion and cloudy swelling. Hydrops of the tubular epithelium was found in dog 34 with much fat in the tubular epithelium

The adrenals were normal except that in dog 34 they showed some hemorrhage into the overlying fat

The series of dogs which were heated more than once included twelve animals. Six were given from two to four exposures and from four hours and fifty minutes to twelve hours and twenty-three minutes. The rise in temperature varied from 64 to 87 degrees. Of these dogs, five died from one minute to two hours after the last heating, and one was killed eight days after the final heating. Dog 29 heated four hours and fifty minutes was found at necropsy to have a diaphragmatic hernia. Four developed severe skin burns (fig 1) and one, dog 28, heated over twelve hours, had a large abscess of the neck

The tissue changes of this group are of much the same order as those in the first group. The organs were congested, but since all but one dog died during the heating, this was probably an acute effect. Cloudy swelling was much less in evidence in the parenchymatous organs. Fatty metamorphosis was also less conspicuous. Glycogen content of liver, kidneys and muscle showed variation, and no conclusions can be drawn except that there was possibly a tendency toward depletion. Dog 89, heated nine times, a total of twelve and one-half hours, showed focal necrosis of the liver, fatty degeneration of the gastric muscle and hemorrhages in the mucosa of the intestinal tract.

Dog 43, given nine heatings, a total of eighteen hours, showed hemorrhages in the adrenals, increased fat in the renal epithelium and megakaryocytes in the splenic pulp. Dog 25 had severe skin burns and anemia and showed foci of rarefaction in the brain. It also had focal bronchopneumonia, hence caution must be used in estimating the effects of the heating.



Fig 1—The axillary region of dog 32 heated twice for a total of ten hours. Due to arcing in a moist surface, a "burn" was produced followed by sloughing in the area shown.

Dog 36, a female bulldog, was given five heatings for a total of nineteen and one-half hours. Several skin burns developed due to arcing, and the dog died six minutes after the last heating. There was still considerable glycogen in its liver. The gastric mucosa was hyperplastic. A papillary carcinoma of the breast showed no degenerated areas such as Schereschewsky found in his transplanted mouse carcinomas. Many megakaryocytes were present in the spleen.

Dog 44 was given the longest period of heating, nine intervals totaling thirty hours and twenty minutes. The rise of temperature was to 107.5 F. The animal was killed with chloroform one hour after the last heating. The pathologic changes did not differ strikingly from that of other dogs. Lymphoid germinal centers were very active. There was no increase in the liver fat. The kidneys were rather hydropic. The testis showed good spermatogenesis. There was arachnoid hemorrhage over the cerebrum. The bone-marrow was hyperactive. Ganglion cells about the adrenals showed vacuolar nuclear changes and migration of chromidial substance to the periphery.

The one outstanding feature of these three series of dogs which were given from one to nine heatings between the plates of the oscillator is the similarity of the tissue changes qualitatively and apparently quantitatively. The hyperthermia produced was about the same in all animals although one degree of difference might have been of great importance to the animal in ways not clearly indicated. It seemed to make little difference whether the dog was being heated for the first or the ninth time. So long as he died during the heating or before his temperature had dropped more than a few degrees, the effects observed varied but little among the twenty-four dogs studied. These animals were of many breeds and sizes, both long-haired and short-haired varieties being represented.

It has been determined by Knudson and Schaible¹ that a dog subjected to this form of irradiation will show a gradual drop to a normal temperature in three hours. There was no tendency toward the development of a persistent hyperthermia following multiple heatings, although individual variation was noted among the animals as to their ability to endure such high temperatures. Evidence of increased cell activity was most evident in the parenchymatous organs, occasionally taking the form of so-called cloudy swelling with or without increase in the rate of cell division as indicated by the number of mitotic figures. Dehydration, which was quite evident in the high viscosity of the blood, was reflected also in the tissues. Breaking down of cells was most evident in the liver where various degrees of fatty degeneration and necrosis were produced and in the lymphoid structures which showed degenerative and necrotic changes.

Twenty-seven adult white rats were subjected to the same form of high frequency heating as the series of dogs. Eighteen animals were heated once the time of exposure in the field fifty minutes to six hours and fifty-four minutes. The normal preheating temperatures varied from 98.2 to 101.8 F. The degree of fever obtained was from 103 to 112 F. The loss of weight was from 2 to 32 Gm., or from 2.1 per cent to as high as 11.2 per cent of body weight. There appeared to be no direct relation between the duration of the heating and the degree of fever the maximum rise being obtained in a few minutes with subsequent heating affecting it little, if at all. There was a more definite relation of duration of exposure to the loss of weight, but exceptions to this were frequently encountered. In other words there appeared to be much difference in susceptibility to heat between individual rats just as there is among man and other animals.

During the experiment the extremities of the rat would usually become hyperemic the nose would 'run,' the mouth salivate, the anal mucosa would swell and the tail expand. In some rats, the tail would sizzle and literally explode the skin of the entire length of the tail being disrupted (fig 2). Gangrene of the tail would later develop usually of the dry type.

Most of the rats were killed by a blow on the head, others with chloroform. The histologic changes in the organs were similar to those in the dogs. Hyperemia, dehydration, cloudy swelling fatty and hydropic changes and focal hemorrhages were widespread. The lymphoid tissue showed much stimulation, and with longer continued heating, necrosis of the germinal centers. A normal gastrointestinal tract was rarely seen. Nematodes were often encountered. Postmortem changes set in early but occasionally necrosis in the crypts of the gastric and intestinal glands with leukocytic reaction was found.

The kidneys liver and heart usually showed marked fatty degeneration. In the liver, the change usually began in the peripheral zone of the lobule. Hemorrhages were frequently found in the adrenal cortex and peri-adrenal fat.

The ovaries appeared normal except for hyperemia. The testes, however, showed marked edema, congestion, occasionally degenerative changes in spermatogonia and spermatids, with proliferation of the Sertoli cells and the formation of giant cells free in the lumen of the tubules. The thyroid and parathyroids showed no lesions.

The brain was examined in several animals killed with chloroform. Hyperemia, edema, subpial hemorrhages and scattered intracortical hemorrhages were rather constant and also chromatolysis in cells of the pyramidal layer.

Glycogen depletion of the liver was moderate in rats heated for short periods and complete after four hours of heating. There was depletion of muscle and renal glycogen also. The bone-marrow was hyperactive in all rats.

Rats 2379, 2380, 2381 and 2382, all males, were heated daily over a period of three months. These animals when killed showed little abnormal. No fatty changes were found. Hyperemia and foci of atelectasis were present in the lungs. There was exhaustion or marked retardation of the spermatogenesis, with exfoliation of the germinal epithelium and proliferation of the Sertoli cells.

Five rats were heated in two or three periods for a total of from three to nine and one-fourth hours. Two developed 'snuffles,' but showed no bronchial

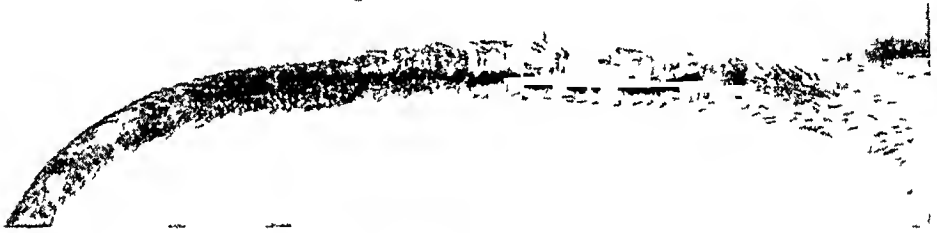


Fig 2—The tail of a rat given one heating of about ten minutes, with rapid rise of temperature. Acute congestion, thrombosis and melting of subcutaneous fat led to rupture of the skin at base of the tail and for much of its length, later followed often by dry gangrene. This injury to the tail is most pronounced when the animal is placed at right angles to the electrode plates during the heating.

or pulmonary changes except congestion. The rest of the organs showed approximately the same conditions as the rats heated but once for periods over two hours.

Three guinea-pigs responded similarly to the rats, a rise of temperature of 8 degrees in one hour being obtained. The tissue changes were similar to those in rats and dogs.

COMMENT

In the foregoing paragraphs we have tried to describe the morphologic picture of the tissues in several types of experimental mammals as seen after the animals had developed a hyperthermia while in the field of a high frequency oscillator. A fair judgment of this mechanism must be based, however, not alone on this descriptive study but also on a comparison with the effects of heat induced by other methods studied with equal care.

Abundant data are available concerning the effects of dry and moist heat externally applied. Diathermy and infra red rays have also been used considerably in recent years. The pyrexia of fever of central

origin would appear to be uncomplicated by infection and hence of value for comparison. The fever of infectious origin, however, includes accessory states such as bacterial toxemia, making a critical analysis of the febrile portion of such disease attended with great difficulty. Nevertheless, since 1917 when von Jauregg introduced malaria into the therapy of paresis, and typhoid vaccine had been used to induce a febrile reaction in the treatment of chronic arthritis, more attention has been given the rôle of fever in clinical medicine. Antipyretic drugs are no longer used as such, being relegated to limbo with "feed a cold and starve a fever" and other obsolete dicta.

Should the reader wish to center his ideas on fever about some one discussion of the subject, he is advised to use the Cartwright lectures on the pathology of fever by Prof. William H. Welch² written in 1888. He reviews the subject thoroughly up to that time and also anticipates most everything that has been experimentally or clinically proved since then.

In his lecture on "The Nature of Fever," Dr. Welch recorded many observations which are worthy of emphasis here. In abstract, he said that fever is an abnormal elevation of temperature. Animals in fever lose weight more rapidly than healthy animals in hunger. There is an enormous increase in the excretion of urea in fever. It is difficult to produce experimentally in animals anything approaching in intensity the well marked fevers of human beings. No definite relation exists between heat production and the height of the temperature. A person usually produces far less heat in fever than he often does under circumstances which normally increase heat production, such as cool environment and muscular exercise. It is impossible to explain fever simply on the basis of excessive thermogenesis. Equilibrium is so disturbed that heat loss does not correspond with heat production. Most animal heat is produced by the muscles.

Concerning "the Effects of Increased Temperature of the Body," Welch stated that high temperature was coming to be regarded as a beneficent provision, *vis medicatrix naturae*, an opinion due in great part to the disappointment over the results of antipyretic drugs. There was no agreement of opinion as to what symptoms were due to high temperature and those due to infection, the high temperature being an index of the severity of the disease rather than a source of danger itself. In hyperpyrexia there is probably complete paralysis of heat regulation, and an analogous condition with similar dangers sometimes develops in animals artificially heated. It is evidently irrelevant whether the source of heat is within or without the body. A mammal artificially heated to

² Welch, William Henry. The General Pathology of Fever, Cartwright Lectures, *M. News* 52: 365, 393, 539, 565, 1888.

111 or 113 F develops convulsions and dies, and rigor mortis occurs promptly. Irritability of the heart muscle ceases, death being due to paralysis of the heart. Naunyn, he quotes, kept a rabbit alive thirteen days with an average temperature of 106.7 F. Welch kept rabbits in a box at 107.3 and 106.6 F three weeks, both lost weight and one when killed showed fatty degeneration of the heart, liver and kidneys. Black and gray rabbits were more resistant to heat than white rabbits. The condition produced by artificial heating, he said, is not directly comparable with fever since in artificial heating loss of heat is reduced to a minimum, the external temperature being higher than the internal. Heat may be abnormally distributed in the body. In fever, infection may lower the tolerance to high temperature. The results of experiments in heat dyspnea in animals cannot be transferred directly to man because in animals respiration has a far more important influence on temperature regulation than in man—a dog pants, a human sweats. Welch noted that the liver first showed fatty degeneration, and then the heart and kidneys. Iwaschkewitsch, Legg and Litten found parenchymatous degeneration in the heart, liver and kidneys.

The forced inactivity of the muscles and imperfect ventilation may have played a part in the experiments. Infection greatly increased the fatty degeneration. The symptoms usually considered those of heart failure are often present in fevers with no visible degeneration in the heart muscle, and vice versa, but often they are associated. Loss of weight is due to increased consumption of tissues and also loss of water. The constipation of fever was explained as being due to the heated blood stimulating the nerves inhibiting peristalsis. There is a general law that within certain limits cell activity is more energetic at high than at low temperatures. Welch emphasized the great necessity of controlling the experimental method by clinical observation.

In the thirty years following the Cartwright lectures, fever came to be regarded more and more as a therapeutic force as is evident from the use of injections of foreign protein in the treatment of chronic arthritis and later by the employment of malarial fever in diseases of the central nervous system.

The structural alterations in the tissues as seen in our experiments with the high frequency oscillator can best be understood if the pathologic physiology is appreciated. Pemberton³ summarizes the effects of external heat as follows: (a) heightened blood flow, (b) increased metabolism, (c) elimination of acids, carbon dioxide, (d) alkalosis, (e) tetany, which may result from the alkalosis, and (f) increase in lactic acid in the sweat. In the pathology of major heat stroke, there

³ Pemberton, R. A Summary of the Effects of External Heat Upon the Human Body, *Am J M Sc* **169** 485, 1925.

are (a) azotemia, due to renal injury, (b) spasm of the left side of the heart, (c) venous congestion, (d) contractions of the intestine and bladder, (e) dilatation of the stomach, (f) cloudy swelling of parenchymatous organs, (g) degeneration of the nerve cells, (h) edema of the lungs, (i) no connective tissue changes, and (j) no ketone acidosis but lactic acidosis

Hot baths, while from time immemorial a popular panacea, have been given more careful study in recent years and their therapeutic scope widened. Mehrtens and Poupirt⁴ noted the effects of hyperpyrexia produced by hot baths on diseases of the central nervous system such as paresis, combined sclerosis, tabes, encephalitis and others. Definite clinical improvement was obtained in many cases. The permeability of the meninges was increased when the temperature was above 103 F and the colloidal gold curve of parietic patients changed to a tabetic curve. The Wassermann reaction of the spinal fluid was frequently diminished. The blood picture tended to show increased hemoglobin and red cell counts and increased reticulocytes.

Von Kennel⁵ found that the normal vesiculation time with cantharides plaster is reduced during the height of fever. He regards the increased permeability of the cells of the body an important factor in the action of modern fever therapy.

In recent years, diathermy has come to occupy a prominent place in physiotherapy and the effects of the heat produced by its relatively low rate of alternating current have been widely studied. King and Cocke,⁶ using a variofrequency diathermy machine at 3,500 milliamperes found that the temperature rises slowly during the first thirty minutes, and then more rapidly to 104.5 F and falls slowly in from six to seven hours to normal. No changes in the blood chemistry were found in several cases so heated. Eight of twenty cases of paresis were improved, and the colloidal gold curve favorably altered. One patient developed acute nephritis at the end of eight treatments, but that the heating was the cause of this is not conclusively shown.

The physiologic effects of currents of very high frequency (from 135,000,000 to 8,000,000 cycles per second) were studied by

4 Mehrtens, H. G., and Poupirt, P. S. Hyperpyrexia Produced by Baths. Its Effect on Certain Diseases of the Nervous System, *Arch. Neurol. & Psychiat.* **22**: 700, 1929.

5 von Kennel, J. Die Permeabilität der Meningen, insbesondere bei der modernen Fiebertherapie, *Deutsches Arch. f. klin. Med.* **165**: 180, 1929.

6 King, J. C., and Cocke, E. W. Therapeutic Fever Produced by Diathermy, with Special Reference to Its Application in the Treatment of Paresis, *South M. J.* **23**: 122, 1930.

Schereschewsky⁷ in 1926. He noted that when small laboratory animals were placed in a box of insulating material and subjected to the action of such a current, severe symptoms were caused which resulted in death when the exposure was prolonged. Part at least of the symptoms were thought due to heat retention. The sequence of events with the exposed animals was as follows. At first, the mouse was quiescent, then agitation began which increased with the length of exposure. The ears, tail and paws turned bright pink, and often became livid or cyanotic as the exposure was prolonged. There was salivation and increased nasal secretion. The head, under parts and paws became moist. After a variable time convulsions and convulsive winking set in with dyspnea. Finally, respiration ceased. The body of the mouse was warm to the touch, and its rectal temperature varied from 42.2 to 44 C (normal from 37 to 39 C).

Death often occurred with a moderate temperature (39.2 C). The primary fatal effect was considered due to the increased body temperature. A mouse killed with carbon monoxide and heated at once with a lethal dose showed little or no rise in temperature, suggesting a heating effect different from diathemy. With the high frequency current in a diathemy apparatus it is easy to raise the temperature of dead tissues well above the point at which albumin coagulates.

Among the sequelae were small hemorrhagic areas along the course of the blood vessels of the ears. In forty-eight hours, the ears became necrotic and fell away. The tail showed ecchymoses, with later gangrene and dropping off. Alopecia of the supra-orbital regions and panophthalmitis sometimes developed.

The effects observed were most marked in a band of frequencies extending from $F = 66 \times 10^6$ cycles to $F = 18.3 \times 10^6$ cycles. Schereschewsky was of the opinion then that, under the conditions of the experiments, there was a differential action with respect to frequency, the lethality of a constant current being in one region of the spectrum inversely, and in another directly proportional to frequency. He stated "since frequency is the sole differentiating characteristic in the whole band of radiant energy it is perhaps to be expected to find that in electromagnetic waves frequency is a determining factor in their mode of action on living organisms."

Schereschewsky⁸ also studied the action of currents of very high frequency on a transplantable mouse carcinoma (Crockett Research

7 Schereschewsky, J. W. The Physiological Effects of Currents of Very High Frequency (135,000,000-8,300,000 Cycles per Second), Pub. Health Rep. **41** 1939, 1926.

8 Schereschewsky, J. W. The Action of Currents of Very High Frequency upon Tissue Cells. (a) Upon a Transplantable Mouse Carcinoma, Pub. Health Rep. **43** 16, 1928.

Lab No 180), a tumor which gave 96 per cent of "takes" and only 2 per cent spontaneous recessions. The limits used were from 66,000,000 to 68,000,000 cycles per second, from 200 to 500 milliamperes. The tumors were implanted at McBain's point, and after a certain amount of growth were pinched between the insulated plates of treatment electrodes. When insulation of the plates was faulty, burns were produced. Softening of the tumors followed exposure in the field. One hundred of 403 mice survived free from tumor. No spontaneous recessions occurred in 230 control mice. The skin showed edema and depilation. The action of the high frequency currents seemed to Scheereschewsky not the same as in diathermy, since with 300 milliamperes and only from three to four minutes exposure there was no significant local heating.

Prof S B Wolbach examined the tumor tissues after their treatment and reported that there was "necrosis of tissue cells and accompanying vascular and connective tissue structures, a coagulative necrosis-like infarction. Extraordinarily rapid disappearance of the tumor. I am quite unfamiliar with anything corresponding to it. Autolysis?" The treatment of the mice appeared to decrease their resistance to infection.

The author mentioned a hypothesis of Prof G W Pierce: "Tissue cells placed in an electrostatic field and subject to the displacement currents caused by the rapid alternations in polarity of the field may undergo some electromechanical vibration which might have definite effects upon the cells."

Kahler, Chalkley and Voegtlin⁹ observed the effect of a high frequency electric field on *Paramecium caudatum*, using 10,000,000 cycles. The temperature of the medium was 30 C. At 41 C, all motility was lost, the organisms became opaque and many disintegrated. No recovery was noted after opacity occurred. No demonstrable effect was seen under sublethal heating either by high frequency or the direct method. There was an identical appearance of the organisms when killed by either way. The chief effect was that of heating due to the rapidly changing electrostatic field.

Carpenter and Boak¹⁰ found that rabbits inoculated intratesticularly with *Spinochaeta pallida* and heated in the same machine as was used in many of our experiments, four, five and seven days after inoculation either failed to develop the primary lesion or showed very slight evi-

⁹ Kahler, H, Chalkley, H W and Voegtlin C. The Nature of the Effect of a High Frequency Electric Field Upon *Paramecium Caudatum*, Pub Health Rep **44** 7, 1929

¹⁰ Carpenter, C M, and Boak, R A. The Effect of Heat Produced by an Ultra High Frequency Oscillator on Experimental Syphilis in Rabbits, Am J Syph **14** 346, 1930

dence of infection. They were of the opinion that the effect on the spirochete is due largely to the heat that is produced within the body.

MacCreight and McKinley¹¹ exposed albino rats in an electrostatic field of 100,000,000 cycles frequency, their study being undertaken because "there is at present a premature trend toward the use of the vacuum tube high frequency generator in therapeutics." They found that death of the animals was accompanied by a violent rush of blood to the fore and hind limbs and tail, which became severely congested and swollen. A comparison was made with the effects of external heat in a dry oven at temperatures of 45, 55 and 65 C, the animals so killed showing no discernible rush of blood to the limbs or tail. It was only when temperatures reaching 160 were used that the effects of external heat were fairly comparable with those obtained in electrostatic fields.

Mellon, Szmanowski and Hicks¹² reported an effect of short electric waves on diphtheria toxin which they regard as independent of the heat factor. A temperature of from 38 to 40 C in a water bath with alternate chillings and heatings did not affect the toxin of the control sample, but the irradiated sample was definitely attenuated in as short a time as fifteen minutes. They suggest that the irradiated diphtheria toxin be investigated with regard to its properties as an immunizing substance.

The question is naturally asked: "Are the morphological or chemical changes in the tissues exposed in a high frequency electrostatic field due to some factor other than heat?" The chemical studies of Knudson and Schaible¹ contain no suggestion of such an influence. Our histologic studies in the dog, white rat and guinea-pig as a whole reveal the usual picture of hyperthermia described as long ago as 1888 by Welch, namely, fatty degeneration of parenchymatous organs, dehydration of tissues, congestion of the organs and focal hemorrhages. Cloudy swelling was probably more marked in our animals than is usually the case with external applications of heat. The degree of congestion obtaining in the appendages leading to thrombosis and gangrene of the tail, ears and feet was a quantitative difference to be carefully considered in the heating of human beings. The acidosis and glycogen depletion also are natural results of intracellular hyperthermia. Other changes such as lymphoid degeneration and necrosis are of the same significance.

The work of Mellon, Szmanowski and Hicks¹² on diphtheria toxin suggests an effect other than that of heat. Their experiments are not

11 MacCreight, J., and McKinley, G. M. The Biological Effects of Temperature Variations with High Frequency Oscillations, *Proc. Soc. Exper. Biol. & Med.* **27** 841, 1930.

12 Mellon, R., Szmanowski, W. T. and Hicks, R. A. An Effect of Short Electric Waves on Diphtheria Toxin Independent of the Heat Factor, *Science* **72** 174, 1930.

exactly comparable with those performed on living cells but nevertheless constitute probably the only evidence so far available of a nonthermal alteration of an organic substance in the field of the oscillator

The ease with which high frequency heating produces congestion of the extremities suggests that it may be of value when cautiously used, in the treatment of certain forms of peripheral ischemia, such as occurs in Raynaud's disease, Buerger's disease and arteriosclerosis

The morphologic changes in the experimental animal so far as our studies go reveal no lesions which cannot be anticipated in the method of using the high frequency oscillator. The dangers are rather obvious, but once understood, experimentation with human disease under proper supervision would seem justifiable. Such work is in progress in the department of medicine of Albany Medical College, under the direction of Dr. Thomas Ordway, and also in other institutions. The results of these lines of investigation should be of great interest.

It cannot be too strongly emphasized that the utmost care be shown in evaluating postmortem changes in animals that have died in hyperthermia. Autolytic changes occur very rapidly. In all experimental studies with heat, the interval before fixation of the tissues should be noted and stated in the reports. The alterations in experimental mouse cancer described by Wolbach in Scheereschewsky's⁸ series suggested acute autolytic processes. In one of our dogs, a papillary carcinoma of the breast was apparently unaffected after five heatings totaling nineteen and one-half hours, a much longer exposure than was necessary to produce definite softening of the experimental mouse tumors.

Another possible danger is the effect of high frequency currents on germinal cells. In the male animals with their testes more or less externally situated, degenerative changes were sometimes produced. It is well known that the male germ cells are very susceptible to heat.

A generalized increase in the metabolic rate of the tissue cells is evident in the parenchymatous organs and also in the bone-marrow which was invariably hyperactive. Whether this fact warrants the use of high frequency electric waves in anemia or leukopenia remains to be proved.

SUMMARY

A study was made of the effects on animal tissues of exposure in the electrostatic field of a high frequency oscillator. Twenty-three dogs, twenty-seven adult white rats and three guinea-pigs were used in the experiment.

A marked hyperthermia was produced in the animals the amount of temperature increase being controllable by altering either the voltage or the distance between the plate electrodes of the apparatus.

The morphologic changes occurring in the tissues were congestion of the organs, peripheral hyperemia, cloudy swelling, fatty degeneration,

dehydration, glycogen depletion focal hemorrhages, especially in the gastro-intestinal tract, epithelial hyperplasia in the parenchymatous organs and stimulation of the bone-marrow. Following prolonged periods of heating, degenerative lesions occurred in the male germinal epithelium.

From a morphologic point of view the alterations observed differ but little from the effects of fever produced by various other methods, but the ease with which the temperature can be controlled in the high frequency field of this apparatus and the character of some of the tissue responses suggest possible therapeutic applications.

HYPERTENSION IN RELATION TO THE BLOOD VESSELS OF THE MEDULLA OBLONGATA^{*}

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Bordley and Baker¹ in 1926 formulated the theory that hypertension was due to arteriosclerosis of the blood vessels of the medulla oblongata. The basis of this theory was formed on the experiments of Anrep and Starling,² who found that a decreased blood supply to the brain causes an excitation of the vasomotor center, which results in a systemic increase of blood pressure. Bordley and Baker believed the location of the vasomotor center to be in the region of the obex. The reason for this conception was an investigation of Ranson and Billingsley,³ who showed, in the cat, that stimulation of the floor of the fourth ventricle seemed to locate the vasodepressor center lateral to the obex and the vasopressor center at the ala cinerea. Because of these experimental observations, Bordley and Baker studied the blood vessels of the medulla oblongata in the region of the obex. In their series, they found that in all the cases of prolonged hypertension there was arteriosclerosis of the blood vessels of the medulla oblongata, whereas in cases with normal blood pressure no arteriosclerosis of the vessels of this region was present. Cutler⁴ in 1928 was unable to substantiate the claims of Bordley and Baker. He found that in some cases of hypertension arteriosclerosis of the vessels of the medulla oblongata was not shown. He studied also the vessels that supply the medulla, but he could not find that in arteriosclerosis there were sufficient anatomic changes of the vessels to suggest a relationship to hypertension.

In the present study the blood vessels of the medulla oblongata in the region of the obex were examined in twenty-four cases of hypertension and in thirty-five cases in which the blood pressure was normal. The

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1 Bordley, J. III, and Baker B. M., Jr. *Bull Johns Hopkins Hosp* **39** 229 1926.

2 Anrep, G. V., and Starling E. H. *Proc Roy Soc, London, s. B* **97** 463, 1925.

3 Ranson and Billingsley. *Am J Physiol* **41** 85 1916.

4 Cutler, O. I. *Relation of Arteriosclerosis of the Cerebral Vessels to Hypertension. Distribution of Arteries Supplying Pons and Medulla*, *Arch Path* **5** 365, 1928.

cases of hypertension that were chosen occurred chiefly in older persons in whom the hypertension was of some duration. In order to compare the vessels in cases of hypertension with the vessels in patients with normal pressure, the medulla oblongata was studied in persons varying in age from 20 to 85 years.

In this report, arteriosclerosis is considered to be of three types. The first of these is arteriosclerosis of the large vessels which is regarded as a connective tissue and elastic fiber hyperplasia of the intima with retrogressive changes. This is arteriosclerosis in the narrow sense, but in the broad sense two other types are included. The second is senile angiectasis, which is a laying down of connective tissue in all the walls of the blood vessels. The third is arteriosclerosis of the arterioles, which is considered to be a hyaline change taking place under the endothelium. Jakob⁵ however, believed that this hyaline change of the arterioles of the central nervous system is found not only in arteriosclerosis but in pellagra, syphilis, chronic intoxication and senility. Aside from the arteriosclerotic changes of the vessels, a reduplication of the elastic fibers was found in the endothelium in a few vessels. Such a reduplication was regarded by Jakob as an indication of syphilis, but since syphilis could not be demonstrated, the change was considered physiologic, owing to advancing age. Sections of the medulla oblongata were taken from the region of the obex. Frozen, paraffin and collodion preparations were made and stained by the usual methods for the study of blood vessels.

OBSERVATIONS IN CASES OF HYPERTENSION

This group was composed of twenty-four cases, in twelve of which arteriosclerosis of more than one vessel of the medulla oblongata was shown. The arterioles in the region of the olives and the larger vessels in the center of the medulla were chiefly affected. According to Cutler,⁴ the vessels in the vicinity of the olives are short and terminate near their entrance along the lateral surface of the medulla, so that it would seem that vascular lesions in the olives would not affect the vasomotor center, since its location is believed to be in the floor of the fourth ventricle.

Of the other twelve cases of hypertension, five showed hyaline change in only one arteriole of the medulla. The important points in one of these cases were as follows:

The patient was a woman, aged 58. Two years before death, she was reported to have an enlarged heart with a systolic murmur at the cardiac apex. The blood

5 Jakob, A. Das Grosshirn, Vienna, Franz Deuticke, 1927.

pressure at this time was recorded as 220 systolic and 110 diastolic. In the next two years the blood pressure varied from 219 systolic and 110 diastolic to 180 systolic and 95 diastolic. Death occurred from myocardial insufficiency. At autopsy marked hypertrophy of the heart and granular atrophic kidneys were found. Microscopic sections of the kidneys showed arteriosclerosis of the arterioles and larger vessels. In the medulla oblongata, one arteriole with a thick layer of hyaline beneath the endothelium was found near the olive.

Arteriosclerotic changes in the vessels of the medulla oblongata were not found in the seven remaining cases of hypertension. Of these, three occurred in men who died from uremia. They varied in age from 31 to 42, and had entered the hospital because of symptoms due to hypertension and chronic nephritis. The arterioles of the medulla oblongata showed only a thickened elastic layer. A fourth case in this group of seven was that of a man of 84 years, whose blood pressure a short time before death from coronary thrombosis was 190 systolic and 110 diastolic. One year previously the blood pressure had been 190 systolic and 90 diastolic. Autopsy revealed an enlarged heart and granular atrophic kidneys, the microscopic sections of which showed arteriosclerotic changes. The media in a few vessels of the medulla was slightly thickened.

Three other patients with hypertension without arteriosclerosis of the vessels of the medulla oblongata died from apoplexy. One was a man aged 71, with mild general arteriosclerosis, another was a man aged 39, with essential hypertension, while a third was a man aged 45, who was known to have had hypertension and an enlarged heart for eight months.

This patient entered the hospital with symptoms simulating tumor of the brain. The blood pressure was 200 systolic and 100 diastolic. Albumin and casts were found in the urine. Ophthalmoscopic examination showed retinitis. Death occurred suddenly after the patient had been a few days in the hospital. At autopsy a fresh hemorrhage at the base of the brain, granular atrophic kidneys and hypertrophy of the heart were found. Arteriosclerosis of the blood vessels of the medulla oblongata was not demonstrable, yet marked arteriosclerotic changes were present in the blood vessels of the kidneys.

OBSERVATIONS IN CASES IN WHICH THE BLOOD PRESSURE WAS NORMAL

Among the thirty-five cases in which the blood pressure was normal, six were found in which one or more blood vessels of the medulla oblongata showed hyaline change. Enlargement of the heart was not present in these cases, but mild arteriosclerosis of the aorta and of the peripheral vessels was found, as well as arteriosclerotic changes in the kidneys, except in case 5, in which there was pyelitis.

Case 1 of this group was that of a woman of 61 years, committed to the hospital because of a psychosis and arteriosclerosis. The blood pressure readings during her few months in the hospital varied from 165 systolic and 70 diastolic to 160 systolic and 70 diastolic. At autopsy generalized arteriosclerosis and atrophy of all organs were found. One large blood vessel with a hyaline change and several smaller ones were present in the medulla oblongata.

Case 2 was that of a man, aged 77. He had been a patient in the hospital for several months because of carcinoma of the stomach. The urine showed a trace of albumin. The three recorded blood pressure readings were approximately 145 systolic and 85 diastolic. In one arteriole in the medulla a proliferation of the endothelium was found, but many showed hyaline change.

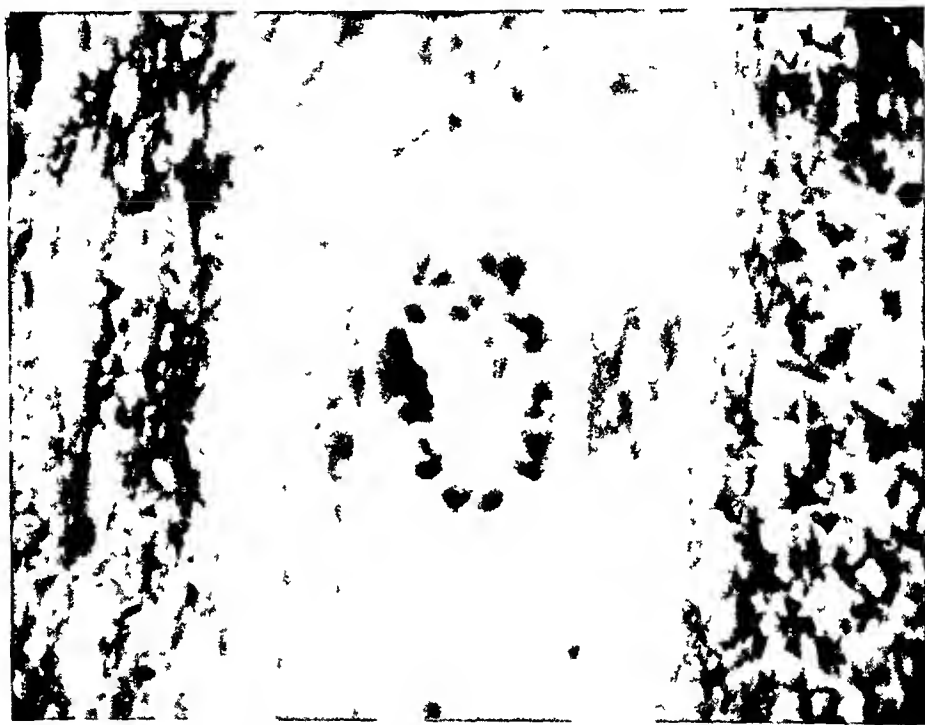


Fig 1—Hyaline change beneath the endothelium of a blood vessel in the medulla oblongata of a woman, aged 61, whose blood pressure was 165 systolic and 70 diastolic. Van Gieson's stain was used, $\times 500$.

Case 3 was that of a woman, aged 65, who remained in the hospital for one year with arteriosclerosis and empyema of the lungs. The blood pressure, taken at frequent intervals, showed an average reading of 100 systolic and 65 diastolic. The arterioles in the medulla were either partially or completely hyalinized beneath the endothelium.

Case 4 occurred in a man, aged 73, who had been in the hospital for many years with involution melancholia. Physical examinations made during that time yielded essentially negative results. The blood pressure readings for the last three years were 155 systolic and 85 diastolic, 130 systolic and 75 diastolic and 120 systolic and 75 diastolic. Shortly before death from a rapidly growing carcinoma of the bladder, the blood pressure was 150 systolic and 60 diastolic. One arteriole in the medulla showed complete hyaline change beneath the endothelium while in many others partial hyaline degeneration was observed.

Case 5 was that of a man of 41 years, who entered the hospital because of diabetes. The blood pressure during several months varied from 125 systolic and 75 diastolic to 110 systolic and 65 diastolic. Death occurred from an ascending infection of the urinary tract. Several arterioles in the medulla oblongata were completely hyalinized beneath the endothelium.

Case 6 was that of a woman, aged 69, who had been in the hospital for many years with a schizophrenic reaction. The blood pressure readings of this patient at the yearly examination for four years previous to death were 110 systolic and 72 diastolic, 128 systolic and 72 diastolic, 140 systolic and 70 diastolic and 134 systolic and 66 diastolic. The patient appeared apparently healthy until difficulty

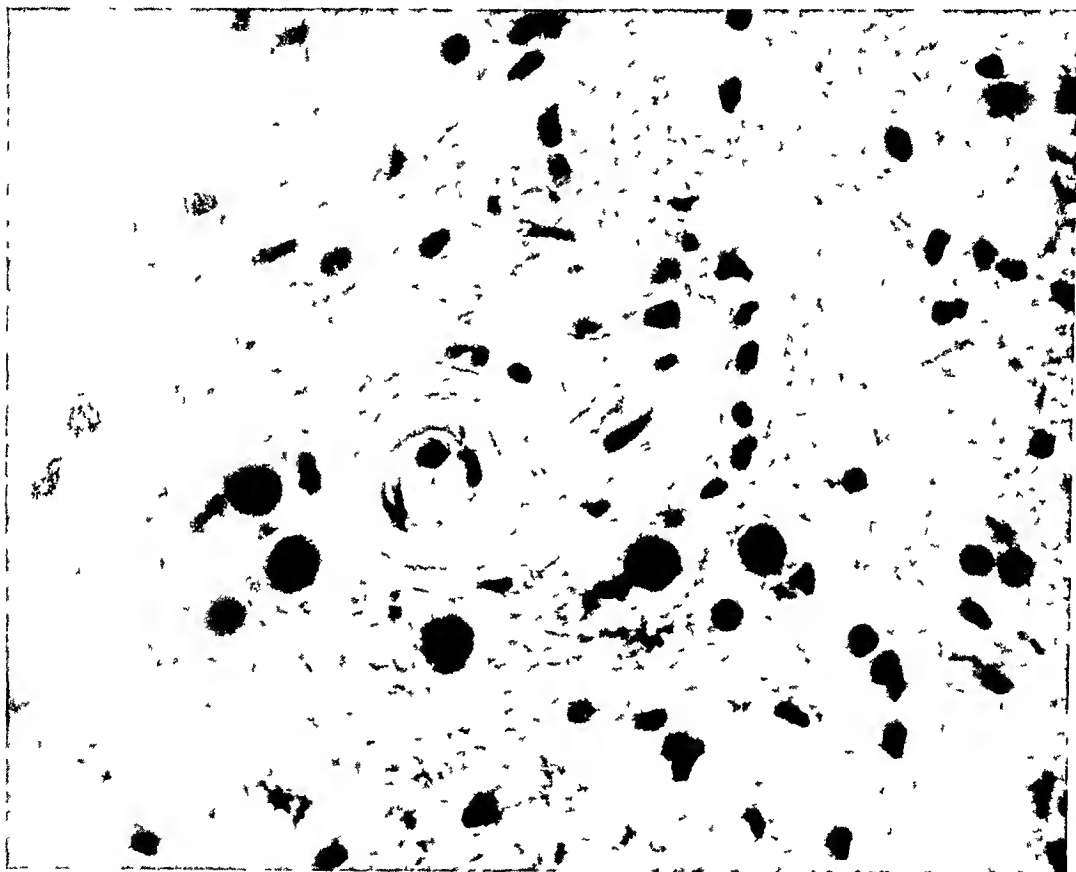


Fig 2—Blood vessel of the medulla oblongata, showing hyaline change beneath the endothelium, in a man, aged 69, whose blood pressure was 142 systolic and 70 diastolic. Hematoxylin and eosin stain was used, $\times 500$

in swallowing developed. Carcinoma of the esophagus was found from which she died in a few months. Three arterioles in the medulla oblongata showed a thick layer of hyaline beneath the endothelium.

Sections of the brain were also examined in this series of fifty-nine cases, but no case was found in which the only vessels showing arteriosclerosis were those of the medulla oblongata, although such an observation would be necessary to prove the theory of Bordley and Baker.

CONCLUSION

The blood vessels of the region of the obex of the medulla oblongata were studied in twenty-four cases of hypertension of varying duration and in thirty-five cases of normal blood pressure. In twelve cases of hypertension, arteriosclerosis of the vessels of the medulla oblongata was found, but in the other twelve cases slight or no arteriosclerosis of these vessels was present. Among the cases of normal blood pressure, six showed arteriosclerosis of the vessels of the medulla oblongata. However, in none of the cases was arteriosclerosis confined solely to the vessels of the medulla oblongata. Therefore, in this histologic study of the vessels of this region no proof is found that hypertension is the result of arteriosclerosis of the vessels of the medulla oblongata.

THE RATE AND LOCATION OF REMOVAL OF BACTERIA FROM THE BLOOD IN HUMAN DISEASE *

REUBEN OTTENBERG, M D

NEW YORK

Numerous experimental observations on animals have shown that bacteria which gain entrance to the blood stream are removed from it with great rapidity

Wysokowitsch,¹ in his classic studies in 1886, injected large numbers of all sorts of bacteria into the blood of rabbits and dogs and showed that both pathogenic and nonpathogenic organisms disappear completely from the blood in a variable time—from seven minutes to three or four hours. Organisms pathogenic for the experimental animal then reappear after some hours and progressively increase in numbers. He carefully proved that there was no excretion of the bacteria by the kidneys or gastro-intestinal tract. In animals killed or dying after from one to several days he showed that many of the bacteria were still alive, and that they were concentrated in certain organs—chiefly the liver, spleen and bone marrow (he did not examine the lungs). He was able to demonstrate bacteria in the endothelial cells of the capillaries of the liver and of the splenic pulp.

Werigo² in 1894, injected anthrax bacilli into rabbits and after a few minutes found that they had accumulated in great numbers in the lungs, where they were mainly engulfed in polymorphonuclear cells in the capillaries. There were many in the liver and the spleen.

Weil³ found that virulent streptococci injected into the blood stream of guinea-pigs are gradually removed by the filtering effect of the tissues. The blood had practically no bactericidal effect. Thus after intravenous injection of bacteria into guinea-pigs the blood showed the following numbers of colonies of bacteria per cubic centimeter at five minutes and at one and a half hours, respectively: 4,000 and 192 in one case, 16,000 and 84 in a second, 4,000 and 612 in a third, and 3,000 and 544 in a fourth. In most cases there was subsequent increase of the number of organisms and death of the animal.

* Submitted for publication Oct 13, 1930

From the Laboratories of Mount Sinai Hospital

1 Wysokowitsch Ztschr f Hyg u Infektionskr **11** 3, 1886

2 Werigo Ann de l'Inst Pasteur **8** 1, 1894

3 Weil Ztschr f Hyg **68** 346, 1911

Bull,⁴ in 1915, injected large doses of pneumococci into the blood stream of rabbits (for which these organisms are highly virulent). In those animals which received simultaneous injections of antipneumococcus serum in another vein, the blood was sterile fifteen minutes later, while in the animals which did not receive serum the blood showed about 1,000,000 organisms per cubic centimeter. (In the animals the blood of which was thus transiently sterilized the organism reappeared in the blood about twelve hours and caused death.) Examination of the organs showed that clumped bacteria were taken up by phagocytes, chiefly white blood cells, but also by endothelial cells. The active white blood cells did not stay in the circulation (confirming an observation of Wysokowitsch,¹) but accumulated in enormous numbers in the capillaries of the lungs, liver and spleen.

Bull attributed this effect to the agglutinative power of the serum and further confirmed this opinion by his work on typhoid and dysentery bacilli. The former are not pathogenic for the rabbit and are agglutinated by rabbit's serum. They are removed very rapidly from the rabbit's circulation. Thus, in one case typical of a number of experiments with typhoid bacilli, the numbers of colonies per cubic centimeter of blood were at one minute, 10,000,000, at two minutes, 2,500,000, at five minutes, 100,000, at fifteen minutes, 40, and at twenty minutes 1.

Hopkins and Parker,⁵ in 1918, injected hemolytic streptococci into cats and rabbits. Immediately after injection in cats the bacteria were more numerous in a given weight of lung than in the same weight of liver or spleen, while in rabbits they were more numerous in liver and spleen. (The same curious difference between cats and rabbits was found by Drinker and Shaw⁶ with manganese dioxide particles injected into the blood stream. They also showed that the particles primarily held in the lungs were, in about eighteen hours, transferred to the liver.)

Manwaring and Coe⁷ offered an explanation of the sudden removal of bacteria from the blood, at least in immune animals. They perfused surviving livers (previously washed free of blood), with pneumococci suspended in Ringer's solution or in normal serum. They found that the organisms came through in practically unchanged numbers unless immune serum was added. As small a concentration of immune serum as 1:1,000 caused complete retention of the bacteria by the liver. The opsonic power of the serum can evidently cause bacteria to be taken up by the fixed reticulo-endothelial cells of the liver, as well as by leuko-

4 Bull. J. Exper. Med. **22** 457, 475 and 484, 1915, **24** 25, 1916

5 Hopkins and Parker. J. Exper. Med. **27** 1, 1918

6 Drinker and Shaw. J. Exper. Med. **33** 77, 1921, **57** 8, 1929

7 Manwaring and Coe. J. Immunol. **1** 401, 1916

cytes Manwaring and Coe found no such effect with lungs, kidneys, intestines or lower extremities of dogs

There have been few direct observations on the removal of bacteria from the blood in human beings. The mechanism as discovered in other animals has been tacitly assumed to apply. Libman and Celler⁸ saw as many as seventy-two organisms per cubic centimeter of blood disappear from the circulation within an hour after resection of the internal jugular vein and operation for sinus thrombosis. Schottmuller⁹ stated that he had frequently seen large numbers of bacteria—as many as 1,000 per cubic centimeter of blood—in the circulation immediately after curettage for septic abortion, only to find the blood sterile fifteen minutes later. In spite of the enormous number of bacteria in the circulation, few cases of invasion of the blood stream ever show metastatic foci—about 2 per cent. Schottmuller stated that entrance of bacteria into the blood stream is of itself one of the most harmless of occurrences—far more innocuous than their entrance into cellular tissue or peritoneum.

In the present paper will be presented data (for the most part obtained for a different purpose) which further indicate that in human disease there is often a rapid filtration of bacteria from the blood.

Four years ago a technic was developed¹⁰ by which blood could be withdrawn safely from the internal jugular veins. The object was to make simultaneous blood cultures from the two internal jugular veins in order to confirm the diagnosis of sinus thrombosis. A very great number of colonies per cubic centimeter of blood in the one jugular vein as compared with the other was regarded as diagnostic of lateral sinus disease. This procedure has now been carried out in fifty-seven cases. In thirty-five of the more recent cases a simultaneous blood culture was also made from a vein of the arm and the number of colonies counted there also, in some cases simultaneous cultures were also made from an artery, and in one instance in which diagnosis lay between osteomyelitis of the femur and acute bacterial endocarditis, the cultures were made simultaneously from the two femoral veins and from a vein of the arm. The results as bearing on sinus thrombosis are presented elsewhere¹¹. The objects in the present paper are (1) to discuss the

8 Libman. J. Michigan M. Soc. **23** 462, 1924. Libman and Celler. Am. J. M. Sc. **138** 409, 1907.

9 Schottmuller. Verhandl. d. Gesellsch. f. inn. Med. **37** 150, 1925. Schottmuller and Binghold, in Mohr and Staehlin. Handbuch der innere Medicine, Berlin, Julius Springer, 1925 vol. 1, pt. 2, p. 786.

10 Ottenberg. Differential Jugular Blood Cultures in Sinus Thrombosis. J. A. M. A. **90** 1602, 1928, Laryngoscope **37** 424, 1927.

11 Ottenberg. Differential Blood Cultures, J. A. M. A. **94** 1896, 1930.

meaning of the large difference which was found in some of the cases of sinus thrombosis between the number of colonies in the vein of the arm and those in one or both jugular veins, and (2) to study the results of the simultaneous cultures from artery and vein

The cases were of two kinds, (1) those (all of otitic origin) in which the vein directly draining the affected area could be aspirated and the number of colonies per cubic centimeter of blood compared with that in other veins, and (2) control cases in which no vein directly draining the lesion could be aspirated, but in which several peripheral veins (and in some instances an artery) were simultaneously aspirated, the latter were chiefly cases of bacterial endocarditis. The cases of otitis are presented in table 1, the control cases in table 2

TABLE 1—*Blood Cultures in Cases of Sinus Thrombosis with Positive Simultaneous Plates from 1 cm of Arm and Both Jugular Veins*

Case	Diagnosis	Colonies of Streptococci per Cc. of Blood		
		Right Jugular Vein	Left Jugular Vein	Vein of Arm
57	Right sinus thrombosis	289	181	23
40	Right sinus phlebitis	165	64	88
41	Mastoiditis, right sinus phlebitis	1½	1	¼
				(femoral vein)
38	Left sinus thrombosis	1	45	27
34	Left sinus thrombosis	9	2	1
	(after operation)	21		5
32	Right sinus thrombosis	250	240	¼
29	Left sinus phlebitis	34	89	9
25	Right sinus thrombosis	600	11	1
23	Mastoiditis plus exposure of right sinus (sinus phlebitis)	24	7	0
9	Cavernous sinus thrombosis	14	70	24
4	Left sinus thrombosis	122	7	6

OBSERVATIONS ON THE DISAPPEARANCE OF BACTERIA FROM THE BLOOD AND EXPLANATIONS

It will be seen on looking over table 1 that in every instance of lateral sinus infection the number of bacteria in the vein of the arm was smaller than in one or both jugular veins. In some instances this disproportion was great, as in case 25 with 600 colonies per cubic centimeter of blood in the right internal jugular vein and only 1 colony per cubic centimeter in the vein of the arm. On the other hand, in 5 cases of bacterial endocarditis the numbers of colonies in the vein of the arm and in the two internal jugular veins were approximately equal. In one case of acute bacterial endocarditis the numbers in the two femoral veins and the cubital vein were equal. And in two cases of sepsis from venous lesions on the trunk the numbers of colonies from the jugular veins and a vein of the arm were equal (table 2)

Two possible explanations might be offered for the small number of bacteria in the distant, as compared with the local, vein in most of

the cases of otitis. It might be due (1) to mere dilution of the jugular blood in the general blood volume or (2) to removal of bacteria at some place in the blood circuit.

The Possibilities of Dilution as an Explanation—How rapidly would bacteria accumulate in the general circulation if they were being fed in at a steady concentration in the internal jugular vein?

This would obviously depend on (1) the volume and speed of the general circulation and (2) the ratio of the blood contributed by one jugular vein to the total venous return to the heart. The former data are well known. To get an approximate idea of the ratio of the jugular to the total venous blood I have measured the jugular veins and the superior vena cava of a cadaver. The circumferences of these veins

TABLE 2—Control Cases

Case	Diagnosis and Organism	Colonies per Cc of Blood		
		Right Jugular Vein	Left Jugular Vein	Ven of Arm
76	Subpectoral abscess, phlebitis of axillary vein, Streptococcus B	1	1	½
55	Cellulitis of perineum, phlebitis of right hypogastric vein, multiple embolic abscesses Staph aureus	3/8	2/8	4/8
52	Acute bacterial endocarditis (femoral culture to rule out osteomyelitis of femur) Streptococcus B	Right femoral vein, 500*	Left femoral vein, 700	500
39	Subacute bacterial endocarditis, Streptococcus A	173	173	260
35	Subacute bacterial endocarditis, Streptococcus A	11	3†	10
20	Acute bacterial endocarditis Streptococcus B	258		252
15	Subacute bacterial endocarditis, Streptococcus A	14	10	16

* Numbers are only approximate, the colonies being too numerous for accurate count but apparently the same on all plates.

† Inaccurate, only one plate from left jugular.

were as follows: internal jugular vein, 16 mm, superior vena cava, 48 mm, and inferior vena cava, 60 mm. From these circumferences the cross-sections of the full veins can be calculated: internal jugular vein, 25.2 sq mm, superior vena cava, 125.8 sq mm, and inferior vena cava, 284 sq mm. If it is assumed that the pressures in the three veins are nearly the same, the relative amounts of blood passing through them should be approximately in proportion to the areas of their cross-sections. The combined area of cross-sections of the superior and inferior vena cava is $126 + 284 = 410$ sq mm. That of one jugular vein is 25.4 sq mm. The ratio between the two $= \frac{25.2}{410} = \frac{1}{16.5}$. The amount of blood returned by one jugular vein in this person then was about one-sixteenth of the total blood returned to the heart in any interval of time.

In an adult whose total blood volume made one circuit per minute (a not impossible figure¹²) the amount of blood passing through the jugular vein in one minute would be one-sixteenth of the total volume. In sixteen minutes the amount of blood contributed by one jugular vein would equal the total blood volume. So that after sixteen minutes, if bacteria were contributed steadily by the jugular vein, the number of bacteria per cubic centimeter of blood in the general circulation should equal the number per cubic centimeter being contributed by the jugular vein, or the concentration in the rest of the blood at this time (if no bacteria were removed) should be one-half the concentration in the jugular vein (since the jugular vein would contain as many as the general circulation plus its new contribution of the moment)

Similarly at the end of a second period of sixteen minutes, the number of bacteria in the general circulation would be twice the number at that moment being contributed by the jugular vein, and so on, in each period of sixteen minutes the number in the general circulation would come closer to that in the jugular vein¹³

If the time of the circulation of the blood were less than one minute (and it generally is, particularly when the pulse is rapid, as in fevers), the time needed for the concentration of bacteria in the general circulation to approach that in the jugular vein would be proportionately shorter

It is evident then that mere dilution will not explain the small number of bacteria found in the general circulation as compared with the number being contributed by the infected vein in some of my cases. Bacteria are evidently killed or very rapidly filtered from the circulation

12 Douglas and Haldane (*J Physiol* **56** 69, 1922) and more recently Burwell, Neighbors and Regan (*J Clin Investigation* **5** 129, 1928) gave the rate of the circulation of blood in adult men at rest as from 5 to 8 liters per minute. With increase in pulse rate (through exercise or fever) the speed increases nearly in proportion to the pulse rate and may be as much as 24 liters per minute. As the total volume of blood in a normal adult is variously estimated at from 4,400 to 5,600 cc (Chang and Harrop *J Clin Investigation* **5** 393, 1928), the round figure of one circuit per minute assumed for the sake of calculation in the text is a not impossible figure. Probably in our patients, most of whom were children and all of whom had high fever, the actual rate was much faster. This, of course, would only strengthen our argument by shortening the time needed for the general peripheral blood to approach the blood of the local vein in concentration of bacteria.

13 It is interesting to compare this figure with the conclusion of Linhard (*Am J Physiol* **77** 669 1926) that after injection of a small amount of a dye solution into a peripheral vein in man uniform distribution throughout the blood occurs in less than five minutes. However, Erlanger (*Physiol Rev* **1** 177, 1921) quoted Douglas as saying that complete mixing takes at least sixteen and a half minutes in man.

The argument to this point has been based on the assumption of a somewhat steady and continuous feeding of bacteria into the blood from the infected focus. However, it has been suggested (Schottmüller,⁹ Martin¹⁴ and others) that bacteria are not given off steadily, but in short "showers." If this were the case one would expect to find such differences as occur in my cases (between the number of bacteria in the blood of the vein directly draining the lesion and that of the vein of the arm) only if one happened, by chance, to take blood for cultures exactly at the moment that the "shower" was occurring. For if one took blood for cultures a few minutes after such a "shower," the blood coming directly from the lesion and containing the bacteria would have passed on and mixed in the general circulation, and one would find a more or less uniform distribution of bacteria in all veins.

As it is unlikely that I should by mere accident have made the blood cultures just at the moment of the "shower" in so many of my cases (for at least seven of them showed a very small number of colonies in the vein of the arm, as compared with the jugular vein or veins), it follows that in sinus infections, at least, bacteria are sometimes fed into the blood stream rather continuously or for fairly long periods of time. It is probable enough, of course, that in other cases or in these cases at other times the "shower" mechanism occurs, indeed, in the preceding paper,¹¹ two cases are discussed in which such a rapid entrance of bacteria into the blood stream was apparently happening at the time of the taking of blood for cultures.

The Points at Which Bacteria Are Possibly Removed—There are no data at hand to indicate just where the bacteria are removed in human infections. On account of the relative slowness of the bactericidal action, even of immune blood, the possibility that all the rapid disappearance of bacteria is brought about by the blood alone can be discarded.

Since all the returning blood must first go through the capillaries of the lungs before reaching those of the other organs, and since the experiments of Wysokowitsch,¹ Werigo,² Bull,⁴ and others show extensive phagocytosis by leukocytes in the lung capillaries, it seems possible that the lungs may be the primary place of filtration, and that (as in Drinker and Shaw's experiments⁶) the transfer to the reticulo-endothelial cells of the liver and other organs may be secondary. There is also a good deal of indirect evidence from experimental introduction into the circulation of leukocytes laden with carmine or other particles, that the lungs act as primary filters (Aschoff,¹⁵ Christeller and Eisner,¹⁶ Seemann and Theodorowitsch¹⁷)

14 Martin, Walton. *Ann Surg* **82** 326, 1925

15 Aschoff. *J Exper Med* **50** 57, 1926

16 Christeller and Eisner. *Beitr Path Anat u z allg Path* **81** 524 1929

17 Seemann and Theodorowitsch. *Ztschr f d ges exper Med* **69** 742 1929

However, even though the circulation of the liver is shunted off from the main blood stream it is possible that the liver may play a primary rôle. The amount of blood passing through it is large. Burton-Opitz¹⁸ found that in a dog weighing 14,300 Gm the liver, weighing 454 Gm, received 422 cc of blood per minute. If one accepts Haldane and Smith's and more recently Linhard's¹³ ratio of the total blood as approximately one-twentieth of the body weight, the blood going through the liver per minute would be actually more than half the total volume. And we know from Manwaring and Coe's⁷ experiments, referred to, how complete the filtration of bacteria by the liver can be. This is borne out for human pathology by clinical observations on pylephlebitis. In this condition bacteria are practically never found in the peripheral blood (Libman¹⁹). The enormous numbers in the portal vein are all filtered out by the liver.

TABLE 3—*Comparative Number of Bacteria in Radial (or Brachial) Artery and in Vein of Arm*

Case	Diagnosis and Organism	Colonies per Cc in Artery	Colonies per Cc in Vein,
39	Endocarditis, Streptococcus A	285	200
38	Sinus thrombosis Streptococcus B	1 or 2	2 or 27*
37	Endocarditis Streptococcus A	6	4
36	Endocarditis Gonococcus	5	3
35	Endocarditis, Streptococcus A	10	10

* This case, which is fully discussed in the preceding paper,¹¹ is given here for the sake of completeness, but is disregarded in the discussion because there was so much delay before the two arterial punctures that the cultures from the arteries were not truly simultaneous with those from the vein. It is regarded as an instance in which a "shower" of bacteria was being rapidly removed from the blood.

Evidence That Peripheral Tissues Are Not Site of Filtration—

While I can offer no evidence as to the particular organs in which the bacteria are filtered out in human disease, I can offer proof that they are not removed by the peripheral tissues of the extremities.

In four cases of bacterial endocarditis and in one of sinus thrombosis, I have done simultaneous blood cultures from a brachial or radial artery and from one or more peripheral veins (see table 3). In these cases the number of colonies in the vein was not significantly smaller than in the artery, i. e., the differences noted were within the range of possible error of the method, and if there was any filtration of bacteria in the capillaries of the hand and forearm it was not detected. I have not made comparative observations on carotid artery and jugular vein or on femoral artery and vein. But since, as pointed out, the six cases of bacterial endocarditis showed approximately equal numbers of bacteria in the two jugular veins and the vein of the

18 Burton-Opitz. Quart J Exper Physiol 4 116, 1911.

19 Libman. Am J M Sc 136 548, 1908.

aim or (in the one case so tested, in the two femoral veins and vein of the arm), and as the two cases of bacteremia from phlebitis of centrally placed veins (hypogastric, axillary) showed the same, it is probable that few bacteria are removed from the blood by the brain and meninges or by the lower extremities

These observations do not rule out a possible extensive removal of bacteria from the blood by the bone marrow, such as has been experimentally demonstrated in animals (Parker and Franke,²⁰ Adler and Singer²¹ and others) In our cases the veins aspirated did not drain a sufficient area of bone marrow to lead one to expect demonstrable effects from this cause

CONCLUSIONS

Observations are presented to show that in cases of sinus thrombosis bacteria are rapidly filtered out of the circulating blood Reasons are given for believing that in many of the cases bacteria are fed into the blood stream from the lesion in the vein somewhat steadily over a period of time rather than in momentary "showers" Observations on the number of bacteria at any moment in the blood of an artery and a vein of an extremity show that there is little or no filtration of bacteria by the peripheral tissues

²⁰ Parker and Franke J M Research **39** 301, 1919

²¹ Adler and Singer Med Klin **210** 429, 1925

General Review

THE PLASMA CELL

A CRITICAL REVIEW OF ITS MORPHOGENESIS, FUNCTION AND DEVELOPMENTAL CAPACITY UNDER NORMAL AND UNDER ABNORMAL CONDITIONS *

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PHILADELPHIA

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The literature on the plasma cell is large and controversial. Downey (1911), Gruner (1913), Ferrata (1918), de Asua (1922), Kingsley (1924), Maximow (1928) and others, including myself (1929), have variously presented accumulated data pertaining to the plasma cell, but in the light of Jordan's recent unique hypothesis that plasma cells are aborted erythroblasts, a detailed presentation of the history of this cell for purposes of orientation seems again to be called for.

Before giving the following survey, I shall call attention to a comprehensive and excellent review on the plasma cell published some years ago in Spanish by Jimenez de Asua (1922). His work and that of Downey, Ferrata, Maximow and myself on the literature may be summarized as follows:

VIEWS OF CAJAL, UNNA AND MARSCHALKÓ

Although not generally known, the plasma cell was discovered and accurately described by Ramon y Cajal in 1890. He encountered the structure in syphilitic condylomas and named it the cyanophil cell, a term still adhered to by the present Spanish school of investigators.

Submitted for publication Jan 20, 1931

* From the Laboratory of the Daniel Baugh Institute of Anatomy, Jefferson Medical College

Priority in using the term "plasma cell" for the same structure belongs to Unna, who, in 1891, used the name in describing a cell seen by him in the skin of patients with lupus. It is interesting to note that Unna himself, in 1903, graciously conceded priority in the discovery of the cell to Cajal.

Cajal originally described the cyanophil cell as a spherical or ellipsoidal structure, varying in diameter from 7 to 14 microns. Its protoplasm was characterized by a deep staining reaction with aniline dyes and the presence of round vacuoles. Its nucleus was pictured as spherical, with a distinct chromatic network and a nearly constant excentric position (*su situación es casi siempre excentrica*). Since, in morphology of nucleus and vacuolization of protoplasm, Cajal was unable to find an analogous type of cell among the then known leukocytes, he was inclined to regard the structure as a special embryonic cell (*Nunca hemos visto en tales células núcleo análogo al de los leucocitos, por lo cual y por su vacuolización protoplásmica nos inclinamos a estimarlos como células embrionarias especiales*).

Regarding the division of the plasma cell, Cajal stated that not infrequently some of these corpuscles might be met with in direct proliferation, but he never saw in them signs of karyokinesis. In 1896 Cajal maintained that the cells were normal constituents of the connective tissue, that they originated from tissue lymphocytes, that the perinuclear area contained a reticular apparatus of Golgi, and finally, that in tumors, epitheliomas and papillomas, the cells could transform into fibroblasts. The latter theory he, however, no longer stressed in his final publications.

Unna (1891), using a technic of polychrome azurine and successive decolorization with glycerin-ether, encountered structures in the skin in lupus, which because of their especially pronounced basophil protoplasm, he called plasma cells, a term which had already been used by Waldeyer (1875) to designate a variety of nonrelated, deep-staining connective tissue cells.

From 1891 to 1908 in various investigations and treatises, Unna insisted that the most salient characteristic of the plasma cell was the deep basophilia of its protoplasm, rather than the specific structure of its nucleus, as Maischalkó in the then current literature repeatedly asserted. The cell according to Unna, was unusually large, oval or cubic in form, its principal characteristic residing in its peculiar protoplasm which, in addition to staining intensely with such basic dyes as methylene azurine and pyronin, showed a constantly present, vague granulation (*amorph-kornig*), which he termed granuloplasm. The latter was regarded as specific for the plasma cell, since other connective tissue cells had an alveolar type of protoplasm (*spongionoplasm*). The nucleus of the plasma cell, usually oval in outline, was depicted as having prevailingly a clear

aspect and a network composed of coarse chromatic strands. Mitosis being rare, the cell divided by amitosis, thereby giving rise to binucleated structures. Genetically, the cell was derived from fixed connective tissue elements by way of unilateral hypertrophy. While, accordingly, a specific type of cell, it, nevertheless, occurred only under pathologic conditions, especially of the chronic variety.

Unna's description of the cell was soon modified by the investigations of Jadassohn (1891-1893), who demonstrated the presence of plasma cells in lymph follicles and lymph glands in man and other animals. He denied the specific character of the granuloplasm and insisted on the paramount importance of a definite chromatic pattern and an eccentric position of the nucleus.

This phase of the problem was preeminently taken up by Maischalkó (1895), for whom the morphology of the nucleus and not the basophilia of the protoplasm (Unna) was the deciding specific criterion for the cell. A granuloplasm did not exist, at most, there was a realization of a mottled (crumbled) aspect of protoplasm (Jadassohn), a condition which he tried to portray by the term "Krumelzellen." After extensive observations on normal, pathologic and experimental material, Maischalko gave the following characteristics as essential for the cell.

- 1 Primarily a specific type of nucleus, small in size, round or oval in contour, with from five to eight distinct, deep staining, angular blocks of chromatin regularly arranged in a circle about the nuclear membrane. (Since this chromatic pattern simulated the disposition of spokes of a cartwheel, Pappenheim later introduced the term "Radkern" to cover the Marschalko type of nucleus.)

- 2 An almost constant, eccentric position of the nucleus (admitted later by Unna)

- 3 A perinuclear lighter staining area, due to an accumulation of protoplasm at the periphery of the cell

- 4 A spherical, at times irregular, protoplasm, which although nonhomogeneous, is, nevertheless, devoid of any specific granuloplasm

The cells, according to Maischalkó, were not pathologic, but normal, constituents of the connective tissue. They did not arise from the latter, but were formed from emigrated hemic lymphocytes, and this for the following reasons. In foci of infiltrations artificially produced, the number of plasma cells was so great, and their appearance so sudden, as to exclude a possible origin from tissue elements. There was an absence of transitional stages between fibroblasts and plasma cells. Lymphocytes, when grouped about the wall of a blood vessel, were so arranged that plasma cells occupied the outermost regions of the infiltration, while lymphocytes were nearest to the vessel. In aseptic reparative processes plasma cells were never seen. In leukocytosis, experimentally produced with tubercular or bacterial proteins,

plasma cells and transitional stages were plentiful in blood vessels. With Biondi staining, the nuclei of connective tissue cells were violet, while those of lymphocytes and plasma cells were green. Finally, according to Marschalko, plasma cells, although a specific type of cell, could transform into fibroblasts, especially in new-formed tissue.

SUBSEQUENT INVESTIGATIONS

The opposing, yet, as it were, guiding, views of Unna and Marschalko gave rise to numerous investigations and frequent polemical discussions. While initially Almkvist (1901) and Schlesinger (1902), later Pappenheim, tried to reconcile the two conflicting theories by the assertion that there were two types of plasma cells, those of Unna and those of Marschalko, subsequent investigations finally led to a precise categorization of the cell as to specific morphology, genesis and functional variation.

The specificity of Unna's granuloplasm, upheld by Downey (1911), was originally denied by Jadassohn and Marschalko and seemingly definitely disestablished by the investigations of Maichand (1913), who showed that a granuloplastic aspect of protoplasm was not peculiar to plasma cells, but due to a transient cytoplasmic basophilia present in a variety of tissue elements other than plasma cells. De Asua (1922), Maximow (1928), Jordan (1929) and others denied the specificity of the granuloplasm, Jordan in particular claiming it to be an artefact. The latter interpretation, however, was not accepted by Gruner (1913), who quoted Schridde as having observed the granuloplasm in frozen sections of fresh tissue. Gruner further quoted Pappenheim to the effect that the granuloplasm consisted of a paranucleoproteid which was "strongly acid, and readily soluble in saline."

De Asua (1922) attempted to solve the problem by asserting that plasma cells were secretory corpuscles, the cyclic changes of which were morphologically expressed in the following types of cytoplasm: (1) pulverized and uniformly basophil (a resting stage), (2) crumbled or mottled (accumulation of secretion in granule form), (3) filamentous (a forerunner to plasmorrhesis) and (4) peripherally serrated (stage of secretion). In addition to these, de Asua recorded two degenerating types, viz., those with vacuoles and those with hyaline body formation.

Recently Kingsley (1924) spoke of a distinct homogeneous granuloplasm in plasma cells. Aside from regarding it as the first sign of the formation of the plasma cell from the fibroblast, he does not commit himself as to its specific nature or significance.

The contention of Cajal and Marschalko that plasma cells are normal components of the connective tissue was soon substantiated by Schottlander (1897) who observed them in the ligament of the normal ovary, by Jolly (1900), Schwarz (1905) and Maximow (1902-1906), all of

whom described them as characteristic structures in the great omentum, and by Dominici (1901) and Schlesinger (1902), who found them abundantly in the intestinal mucosa. Since then, various workers, especially Maximow, Feriata, Weidenreich, Downey and Jolly, have shown them to be normally present in the interstitial tissue of various organs and glands (mammary and submaxillary glands, tonsils, liver, kidneys, bone marrow and lymphoid tissue). Few in the circulating blood, normal or pathologic (Feriata, Piney), sparse in loose connective tissue (Maximow), their presence in the embryo was denied by Schüdde (1921), Feriata and myself (1923) and Maximow (1928).

THE CELL IN LOWER VERTEBRATES

Respecting lower vertebrates, Soluch (1908) showed that plasma cells are abundantly present in the connective tissue of birds, an observation recently confirmed by Mjassojedoff (1926) for the adult hen. Downey (1911) reported high ratios of plasma cells, many of which were atypical and of clasmatocytic origin, in amphibia, reptiles and fishes. He found them to be particularly numerous in the lymphorenal tissue of the ganoid fish polyodon, in the lung of the garter snake and in the mesentery of the frog. I examined many species of cold-blooded animals, and contributed data (1924) which indicated an apparent absence of the plasma mast cell in lower forms. According to Jordan and Sperdel (1929), plasma cells are numerous in the splenic sinuses of the horned toad.

THE PERINUCLEAR AREA

Theories regarding the nature of the perinuclear lighter staining area (astrospheric region) in the plasma cell varied considerably. Maischalko considered it as an essential criterion of the plasma cell. Unna, however, contended that, since it was caused by a washing out of granuloplasm, all cells having such an area were in a state of incipient atrophy, a point of view confirmed later by Greggio (1909) and Papadia (1910). Joannovics (1899) and Schaffer (1910) maintained that the area represented a portion of the cytoplasm devoid of basophil substance, an interpretation somewhat similar to that of Dubreuil (1909), who claimed that the perinuclear cytoplasm was homogeneous and vitreous. The most probable opinion, viz., that the area constitutes the specific sphere of attraction of the cell, with content of centriole group, was first established with iron-hematoxylin staining by Maximow (1902-1906) and subsequently corroborated by Weidenreich (1909), Wallgren (1911), Jolly and Feriata. Cajal (1896), as stated, had shown that this area contained a distinct Golgi apparatus. Downey (1911) regarded the area as the seat of initial elaboration of fuchsinophil bodies. Gruner

(1913) quoted Pioell as having observed lipid granules in the astrospheric region, also Loele as recording the presence of much phenolphthalein substance near the nucleus

VACUOLLS

Cytoplasmic vacuoles in plasma cells, originally noted by Cajal, were later shown to vary in number, content and distribution. Some investigators interpreted them as degeneration phenomena (Unna, Kiompecher, Papadia, de Asua), others regarded them as representing temporary secretory cell states (Weidenreich, Downey). Their nonartificial nature was established by Dubreuil and Favre (1920) in staining them supravitaly with neutral red. Dubreuil (1909), later Dubreuil and Favre (1920), also Wallgren (1911), Downey (1911), Schridde (1929) and Bloom (1928), demonstrated in these vacuoles the presence of round, granular or rod-shaped structures (mitochondria, Schridde-Altman granules). According to Bloom (1928), the presence of a typical well developed rosette in the plasma cells, revealed with supravital neutral red staining, "deprives the rosette of its importance as a specific criterion of monocytes," as claimed by Cunningham, Sabin and Doan (1925). Recently Forkner (1930), after examining supravitaly stained preparations of lymph nodes of rabbits, repudiated Bloom's observation, stating that in no instance do plasma cells possess the segregation granules characteristic of monocytes.

DIVISION

Regarding mitotic division of plasma cells, Cajal first stated that this took place very rarely, an opinion confirmed by Unna, Ferrata, Kiompecher, Maximow, Globus and myself and others. Maximow and Globus and I asserted that when such a division did occur, it was nearly exclusively in young plasma cells. Schridde (1921), on the other hand, seemingly held mitosis as frequent, especially in the plasma cells of perivascular infiltrations.

Indirect division, i. e., amitosis or amitotic constriction of nucleus with resultant binucleated or trinucleated structures, has repeatedly been reported as a frequent phenomenon in plasma cells (Maximow, Weidenreich, Downey, Dubreuil and Favre, de Asua, Globus and myself). Maximow (1902) regarded the process as peculiar to old, i. e., degenerating, cells, an observation which I also made on the cells in perivascular infiltrations.

According to Ferrata, direct nuclear division without accompanying cytoplasmic division explains the origin of the large multinucleated (from five to eight) plasma cells, originally referred to by Cajal. On the same basis Kiompecher explained the formation of giant plasma cells, the existence of which was also admitted by Ferrata.

ATYPICAL PLASMA CELLS

References to the literature have thus far in this review concerned typical plasma cells. On the occurrence of atypical plasma cells, a point especially emphasized by Weidenreich, Downey, Pappenheim, Naegeli and Maximow, the following observations are to be listed. As early as 1895 Hodara grouped basic staining cells into plasma cells and pseudoplasma cells. This procedure was followed by Papadia (1910) in his large work on experimental encephalitis, in which even endothelial cells were reported as displaying a plasma cell aspect, but because of nuclear differences were termed pseudoplasma cells.

Pappenheim (1901-1920) perhaps reached the greatest extreme in claiming that all lymphoid cells, whether of lymphoblastic or myeloblastic origin, may transform into plasma cells (plasmocytes), hence his intricate, practically self-guiding terminology of macrolymphocytic plasmocyte, leukoblastic macroplasmocyte, lymphocytic micropasmocyte, microleukoblastic plasmocyte, etc. Guenei (1913), adopting Pappenheim's view, gave a similar list of possible plasma cells. In another posthumous work (1919) Pappenheim textually (p. 188) stated that plasma cells are to be regarded as inflammatory, altered histogenous lymphocytes of granulation tissue (*entzündlich veränderte histogene Granulationsgewebslymphocyten*). In spite of this seemingly restrictive categorization, in the same work are depicted many figures of plasma cells which include manifold transitional stages from lymphocytes and monocytes, leukoblasts and lymphocytes to plasma cells.

Opposed to the extreme position of Pappenheim, Maximow (1902), Schwaiz (1905), Weidenreich (1909-1910) and Downey (1911) maintained that atypical plasma cells may differentiate from a restricted quota of lymphoid cells (polyblasts, lymphocytes, clasmatocytes), Weidenreich perhaps coming closest to the contention of Pappenheim with the statement that since the plasma cell condition (*Plasmabeschaffenheit*) is a transient, functional, i. e., irritative, physiologic condition, it may occur in various lymphoid cells, perhaps even in lymphoblasts. Downey (1911), in a comprehensive study of plasma cells, adopted a similar view, stating that "plasma cells are differentiated from all types of lymphoidal cells." Convinced on comparative cytologic evidence that there are plasma cells having morphologic characteristics other than those given by Marschalkó, he included as additional precursors of plasma cells, the perithelial cells of Maichand, the resting wandering cells of Maximow (clasmatocytes), the large leukocytoid lymphocytes, the large mononuclears (even those coming from the mesothelial cells of the mesentery) and possibly, a small percentage of fibroblasts.

Supporting Pappenheim's view are the views of Schridde (1902), Guenei (1913), Huebschmann (1913), Naegeli (1919), McGowan

(1928) and Piney (1928), all of whom admitted the occurrence of typical lymphoblastic plasma cells as originally stated by Hodara. Turk went still farther by including as plasma cells his "irritation forms," cell types usually regarded as pathologically altered myeloblasts (Naegeli, 1919). Gruner (1913) adopted Turk's view in claiming that the irritation forms are tissue plasma cells which entered the blood stream. Recently Downey (1924-1928) in an extensive study on the myeloblasts, admitted a differentiation of plasma cells from myeloblasts, but stated that while the nuclear pattern of the latter may remain unaltered during the transformation, "frequently its chromatin becomes exaggerated into coarse masses and then it is difficult to tell whether the plasma cell has been derived from a large lymphocyte or a myeloblast."

That the "irritation forms" of Turk, described by him as characteristic for pathologic, especially leukemic, blood, have no relation to plasma cells was, in the opinion of Feriata, definitely established by two of his pupils, Juspa and Negreiros-Rinaldi (1913). In studies of blood and bone marrow they demonstrated the nuclear differences in the two types of cells, interpreting the "irritation forms" as developmentally inhibited hemocytoblasts. It was further shown by Feriata and myself (1923) that the occurrence of Turk cells, as well as of Rieder cells, is not necessarily restricted to pathologic conditions, since both types may be encountered as normal constituents of embryonic blood, viz., that of the prehepatic period. Because of the extreme sparsity of Turk cells, Naegeli suggested that the term "irritation form" be dropped.

Seemingly still dubious is the position of the lymphoblastic plasma cell. Foa (1902), in a case of typhus encountered lymphoblast-like plasma cells in splenic follicles, but regarded the reaction as pseudo-plasmatic since in respect to nuclear morphology the deep-staining cells in no way corresponded to plasma cells. Naegeli (1919), on the other hand, selected lymphoblastic plasmic cells as one kind in a classification of four possible types (the others being lymphocytic, "Radkein" and myeloblastic). In the blood of patients with measles he observed 30 per cent lymphoblastic plasma cells and quoted Hildebrandt as having reported 17 per cent for the same malady.

Of paramount importance in this respect is the position taken by Feriata. In his large work he repeatedly emphasized the fact that if deep basophilia of protoplasm alone is considered the specific criterion of the plasma cell, then one can equally well include in this category various unrelated lymphoid cells, even the progenitors of the erythrocytes. (Con questo criterio allora una grande quantita di cellule a tipo linfoide, compresi i progenitori degli eritrociti, potrebbero venire confuse colle plasmazellen.)

The quotation brings me to the most recent speculations regarding the plasma cell. Thus McGowan (1926-1927), on the assumption that the term plasma cell is "rather a morphological than a physiological one," postulated the formation of lymphoblastic, monoblastic, myeloblastic and even erythroblastic plasma cells by way of aberration from primitive stem cells. Jordan (1929) and Jordan and Speidel (1929) and presumably Dawson and Masui (1929) interpreted plasma cells as aborted hemoblasts, i. e., erythroblasts or granuloblasts that failed to differentiate into normal red corpuscles or granulocytes. In contrast to these writers Piney (1928) followed the commonly accepted interpretation that plasma cells are modified lymphocytes, but postulated the occurrence of lymphoblastic plasma cells under morbid conditions.

ORIGIN OF PLASMA CELLS

As opinions have varied in respect to the specific morphology of the plasma cell, so likewise have they differed as to its histogenesis. The theories advanced may be briefly summarized as follows:

1 A histogenous origin from connective tissue cells, including tissue lymphocytes, fibroblasts, clasmatocytes, resting wandering cells, adventitial cells, hemohistioblasts, etc. Unna (1891), Cajal (1896), Pappenheim (1901-1920), Marchand (1901), Dominici (1901), Foa (1902), Turk (1904), Morandi (1904), Verratti (1905), Ehrlich (1904), Greggio (1909), Papadia (1910), Downey (1911), Ferrata (1918), de Asua (1922), Lewin (1929), Rogers (1930) and Kingsley (1924). Kingsley emphasized especially a fibroblastic origin, since Downey (1911) had stated that "the plasma cells formed in this way are not numerous and it is still a question as to whether they ever develop into the typical Marschalko type."

2 A hematogenic origin from emigrated lymphocytes. Marschalko (1895), Schottlander (1897), Krompecher (1898), Else von der Leyen (1901), Enderlen and Justi (1901), Schlesinger (1902), Nissl (1904), K. Ziegler (1904), Cerletti (1907), Naegeli (1919) and Jolly (1923).

3 Mixed origin from emigrated lymphocytes (monocytes) or pre-existent tissue lymphocytes. Ribbert (1897), Joannovics (1899), Maximow (1902), Schridde (1905-1921), Weidenreich (1911), Downey (1911), Dubreuil and Favre (1920), Bloom (1928), Globus and myself (1929).

4 An origin from immature blood cells (myeloblasts, hemoblasts [erythroblasts, granuloblasts]) through aberration or abortion. McGowan (1928), Jordan (1929), Jordan and Speidel (1929) and Dawson and Masur (1929).

Regarding tissue cultures, Maximow (1922-1923) showed that in explants of lymphoid tissue plasma cells develop from local lymphocytes in the course of two days. In cultures of leptomeninges the same phenomenon was noted, being particularly marked in lymphocytes having a periaxial habitat.

PROGRESSIVE AND REGRESSIVE CHANGES IN PLASMA CELLS

Degenerative Changes—Russell Bodies—In summary, the degenerative changes recorded in the literature have been the following

1 Homogeneous Degeneration This process is characterized by an uneven, varying feeble staining capacity, at times a nonstaining capacity, on the part of the cytoplasm of the plasma cell, while the nucleus remains relatively intact. According to Unna, it is accomplished through separation of the granuloplasm and fragmentation of the spongionoplasm. For Schridde, Maximow, Jolly, Kingsley, Globus and myself, degeneration is the ultimate fate of the vast majority of plasma cells. They are brought into existence only to undergo degeneration, the associated phenomena of which are pyknosis and fragmentation of nuclei, with frequent formation of acidophil bodies.

2 Hyaline Degeneration This is exemplified in the formation of intracellular hyaline (acidophil) bodies, commonly known as Russell bodies (1890). Unna spoke of the phenomenon as a hyaline metamorphosis of the granuloplasm effected by a combination of the acid substance of the latter with a basic albuminoid substance present in the interstitial lymph. This opinion, confirmed by Fick (1908), was objected to by Papadia (1910), who stated that since in number and in mass the hyaline globules far exceed the protoplasmic dimensions, their origin is perhaps due to a cytoplasmic pathologic secretion, which on accumulation is extruded. Gruner (1913) cited Miller (1910) as considering Russell body formation to be a myelin degeneration of cell substance.

Numerous workers, Pappenheim, Ferrata, Jolly, Maximow, Downey, Schridde, de Asua, Kingsley, Jordan and Speidel and others, including myself, showed that Russell body formation is a constant phenomenon in degenerating plasma cells, and that at necrobiosis of the latter the bodies become freely dispersed into the tissues. In syphilitic material these acidophil bodies were shown to vary in size from small eosinophil, granule-like structures to giant spheres of monocyte proportions (Globus and myself). According to Schridde (1921), Russell bodies make their first appearance in the form of fine bluish, gentianophil granules, which then through growth and confluence give rise to the larger and more characteristic structures. With safranin and methyl green staining, according to Pappenheim (1919), the bodies appear red in a background of green. Downey (1911) gave similar pictures.

That Russell bodies are pathologic secretions of plasma cells was recently again advocated by de Asua (1922). According to Downey (1911), the structures "probably represent a special kind of secretion or the accumulation and thickening of the normal secretion," a view likewise recently suggested by Kingsley (1924). Decidedly new was the speculation of Jordan and Speidel (1929), according to whom Russell

cell bodies "represent hemoblasts (erythroblasts or granuloblasts) which failed to transform normally into erythrocytes or granulocytes" Dawson (1929) was inclined to favor a similar view

3 *Vacuolar Degeneration* This process, noted by Cajal, Unna, Pappenheim, Kiompecher, Papadia, de Asua and others, is characterized by the presence of unstainable areas, which give the cell a foamlike aspect, hence the term "Schaumzellen" employed by different authors (Pappenheim) Schüdde interpreted the process as a mucoid degeneration, while Unna and Papadia regarded it as due primarily to a change in water content Since this type of degeneration was reported as frequent in condyloma (Cajal), likewise in dementia paralytica (Fianca and Athias, 1902), Pirone (1909) suggested that it was peculiar to aged cells In Pappenheim's last work, "Schaumzellen" are regarded as former histogenous phagocytic monocytes from which the Russell bodies have become extruded

4 *Pathologic Degeneration* Kiompecher stated that pathologic degeneration occurs especially during inflammatory processes and is characterized by important nuclear changes, viz, vesicular aspect, uniform color a less distinct chromatic network, with one or two central blocks In the opinions of Bosellini and Papadia, it was the viewing of this type of degenerating nuclei in lupus material which prevented Unna from properly evaluating the essential importance of nuclear structures as outlined by Maischalkó

5 *Hemoglobiniferous Degeneration* The hypothesis of Jordan, Jordan and Speidel, and, presumably, of Dawson, of a hemoglobiniferous degeneration is based on the view that aborted erythroblasts become plasma cells and as such gather the initially elaborated hemoglobin into globules, thereby forming Russell bodies McGowan's theory may be incorporated under this heading, for the aberrated erythroblastic plasma cell, according to him, has hemoglobin in its cytoplasm A genetic relationship between plasma cells and erythroblastic formations was denied by MacMillan (1928) and Forkner (1930) The former found no evidence for it in lymph nodes of rats rendered anemic, Forkner contended that although plasma cells in supravital stained preparations of lymph nodes have a homogeneous protoplasm exhibiting a faint yellow tinge similar to that existent in developing red cells, the conclusion cannot be drawn that, therefore, they are developing erythrocytes, since other criteria distinguish them from the latter

Progressive Changes—Plasma Mast Cells—The following developmental potencies have been ascribed to plasma cells

1 *Formation of Plasma Mast Cells* This process, accomplished through an endogenous differentiation of basophil, metachromatic gran-

ules in otherwise unaltered plasma cells, was first reported by Kiömpecher (1891), who observed it in mammary cancer and endotheliomas of the skin. The observation was subsequently confirmed in various other material by Maischalko, Schwarz, Weishaupt, Pappenheim, Weidenreich, Downey, Sabrazes and Lafon, Martinotti, Greggio, Weill and others. Of recent workers, Ferrata (1918), Schüdde (1921) and de Asua (1922) denied the formation, while Dubreuil and Favie (1920) and Globus and myself (1929) reaffirmed it.

2 Elaboration of Other Granules. Thus, according to Schüdde (1905), a very large proportion of plasma cells elaborate neutrophil granules, 1 in 1,000 develops eosinophil granules, while 1 in 2,000 forms basophil metachromatic granules. Regarding the latter, Schüdde, in a recent contribution (1921), asserted that cells having the cartwheel nucleus and basophil granules are not to be classified with plasma cells, i. e., they are not plasma mast cells, but ordinary mast cells the nuclei of which have undergone peripheral hyperchromatic changes similar to those seen in erythroblasts and various other cells. In the same work, Schüdde maintained that, while the majority of plasma cells contain Altman granules, a certain quota have fine bluish gentianophil granules, the precursors of Russell bodies. Naegeli's opinion, viz., that some plasma cells contain azure granules, was denied by both Pappenheim (1920) and Ferrata. Dubreuil and Favie described, in certain plasma cells, eosinophil granules, in others secretory granules similar to those found in gland cells.

3 Transformation of Plasma Cells into Fixed Connective Tissue Elements. Marschalkó held the transformation of plasma cells into fixed connective tissue elements to be true, especially in new-formed tissue, an opinion shared by Gruner (1913), who claimed that with scar formation the local plasma cells become fibroblasts. Cajal reported transitional stages leading to the formation of fibroblasts in tumors, papillomas and epitheliomas. Whereas, in his last publication Cajal was inclined to doubt this developmental potency, de Asua (1922) seemingly reaffirmed it. Schottlander and Kiömpecher, although both advocates of a hematogenic origin of plasma cells, stated that the latter could transform into fixed connective tissue elements and epithelioid cells, a theory fully subscribed to later by Ravenna (1906). Recently, Kingsley (1924) admitted a heteroplastic development of plasma cells from tissue lymphocytes and fibroblasts, but denied a reversion of such formed plasma cells to parental stages.

SPECULATIONS ON FUNCTION

Joannovics (1899) and Schaffer (1901) contended that since plasma cells appear wherever there is destruction of nuclei their formation is

due to local absorption of chromatic material, incidentally, they thereby help to remove cellular metabolic products

Bosellini (1902) advocated the quaint theory that the stainable material in plasma cells is nucleic and destined for the formation of new nuclei

Enderlen and Justi (1901), also Poicile (1904), believed that the cells were carriers of nutritive material, a point of view partially taken by Dantschakoff (1905) in maintaining that in the submaxillary gland plasma cells, after absorption of substance from the blood and lymph, transmit it to epithelial cells. At one time, Pappenheim (1905) interpreted the formation of plasma cells as caused by a pathologic over-nourishment (hyper trophy) in connective tissue cells. Recently Kingsley (1924) favored a similar view. On the hypothesis that the peculiar appearance of the granuloplasm of the plasma cell is due to iron content (Harris), Gruner (1913) suggested that the iron in question might possibly "bear some relation to the formation of fibrous tissue secretion."

Weidenreich (1909-1911) proposed the solution that the pronounced basophilia of plasma cells is due to a transient, nutritive physiologic condition in lymphocytes, that the cells are secretory corpuscles, as evidenced by extensive cytoplasmic budding and loss of these by clasmatosis to adjacent tissues. Downey (1911) confirmed this point of view, especially for the plasma cells in lower vertebrates. De Asua (1922) upheld it as true for all plasma cells, save those exhibiting vacuolar and hyaline degeneration.

Huebschmann (1913) regarded plasma cells as elements capable of elaborating a defence (antitoxic) substance. A similar view was propounded by Klein (1914) and by Aineh (1920) in maintaining that plasma cells, especially those of chronic disturbances (paralysis, meningitis), are not degenerating cell forms, but functional states of lymphocytes, which, through local toxic activation, are intimately related to immunization processes. Kingsley (1924), on the basis of the large aggregates of plasma cells found in degenerating areas and their mode of origin from local tissue elements, explained their presence as a possible reaction phenomenon, produced by local metabolic changes.

A phagocytic power was ascribed to plasma cells by Nissl (1904), Vanzetti and Parodi (1905), and Gruner (1913). This was denied, however, by Marchand (1902), Moirandi (1904) and Gioggio (1909).

PATHOLOGIC CONDITIONS

Much of present knowledge regarding plasma cells has been obtained from studies on pathologic material, for the simple reason that, under morbid conditions, especially of the chronic inflammatory type (infiltrations), a marked increase of plasma cells usually takes place. Specific

instances of such increases were listed by the following Unna (1891), Jadassohn (1891) and Almkvist (1901), in lupus material, Unna (1891) and Bosellini (1902), in granulomas of the skin, Cajal (1896) and de Asua (1922), in tumors, epitheliomas and papillomas, Economo (1920), Marcoia (1921) and Globus and myself (1927), in the central nervous system in various forms of encephalitis, Papadia (1910), Vanzetti and Parodi (1905), in those experimentally produced, Foa (1902), in typhus, de Asua (1922), in tuberculous material, Franca and Athias (1902), Havet (1902), Alzheimer (1904), Nissl (1904) and Globus and myself (1929), in the perivascular infiltrations of dementia paralytica, Rogers (1930), in solitary plasma-celled myeloma of bone marrow, Grawitz (1911) and Pappenheim (1919), in the blood of chronic lymphoid leukemia, Klein (1914) and Arneith (1920) in disturbances of the cerebrospinal fluid, Naegeli (1919), in the blood of patients with measles, in which an increase of plasma cells to 30 per cent was recorded.

This topic may be concluded by again referring to the respective positions taken by Maximow, the anatomist, and Naegeli, the pathologist. Maximow repeatedly asserted that wherever an aggregation of lymphocytes and monocytes occurs, there likewise a varying proportion of plasma cells, with transitional stages from lymphocytes and monocytes, may be met with. Naegeli, sharing Maximow's opinion that most plasma cells are modified lymphocytes, recorded them as ubiquitous structures in perivascular infiltrations, granulomas, tumors, etc. A predominance of plasma cells may, in his opinion, lead to (1) a plasma cell lymphoma, either local or generalized (Frank [1913]). (2) a multiple myeloma of the bone marrow or (3) a specifically distinct plasma cell leukemia, with systemic involvement of the hematopoietic system. In support of the latter view, Naegeli referred in particular to the two cases noted by Ghon and Roman (1913), one of which showed 50 per cent plasma cells in the bone marrow. To these may be added, according to Grawitz (1911) and Gruner (1913), the leukemias of plasma cell type reported in the literature by Gluzinski, Reichenstein, Lusksch, Foa and Michaeli.

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Notes and News

Plant Pathology in the Rockefeller Institute—The Institute has established a division of plant pathology in connection with its branch for animal pathology near Princeton, N J The new division will be in charge of L O Kunkel who has been pathologist at the Boyce Thompson Institute for Plant Research at Yonkers, N Y The combined laboratories will be known as the Department of Animal and Plant Pathology of the Rockefeller Institute for Medical Research

Isaac Adler Prizes for Medical Research—It is reported that Harvard University has been willed \$20,000, the income of which is to "provide once in three years a prize for the best piece of original research produced within that period in the United States or Canada on any subject within medical or allied sciences"

New Laboratory at Rockefeller Institute—This is a seven story structure with two basements which is connected by tunnels with other buildings of the Institute Five sections of the division of pathology and bacteriology occupy space in the new building

Anna Fuller Fund—According to *Science* for April 3, 1931, the "will of Egbert C Fuller, president of the E C Fuller Company, of New York, who died at New Haven on March 5, provides for the establishment of a fund which the executors estimate will reach \$1,500,000 to be used 'for alleviation of suffering from disease and especially for the control of cancer' Mr Fuller, in his will, directed that the fund be known as the Anna Fuller Fund, in memory of his wife, who died from 'this painful disease' The fund may be used according to the will only for research as to its cause, treatment and care, the education of the public as to its prevention and treatment and the actual treatment of persons suffering from the disease While there is hope of preventing cancer, Mr Fuller provides in his will that the fund shall not be used for the treatment of persons suffering with the disease 'except as incidental to such research and education' The will also provides for the creation of the Anna Fuller memorial prize which is to be given to any person or persons who 'make a real and outstanding contribution to knowledge of the cause, care and prevention or cure of cancer' Such award or awards shall not in any five-year period exceed the sum of \$25,000 Prizes are to be awarded upon the recommendation of the president of the American Medical Association, the dean of the Johns Hopkins Medical School and the dean of the Harvard Medical School"

New Quarters for Department of Pathology of Long Island College of Medicine—These quarters consist of communicating floors of the old Hoagland laboratory and the new science laboratory This space is occupied by the Murray Museum and by preparation and staff rooms The new students' laboratory is situated on another floor of the new building A new morgue with a miniature amphitheater seating fifty has been completed and is so designed that the eyes of the furthest spectator are only 13 feet from the table

DOCTORATES CONFERRED IN HUMAN AND ANIMAL BACTERIOLOGY AND PATHOLOGY BY AMERICAN UNIVERSITIES, 1929-1930

Callie Hull and Clarence J West, Reprint and Circular Series National Research Council, no 95, 1930

Brown Edwin Munroe Knights, "Observations on Hemolytic Streptococci in Scarlet Fever"

California James Duncan Brew, "Policies and Results of Sanitary Milk Control"

Chicago Paul Hardin Harmon, "Observations on the Inoculation of the Smaller Laboratory Animals with the Poliomyelitis Virus" Roland Wendell Harrison, "Experimental Studies upon the Etiology of Influenza" Daniel Allan MacPherson, "Studies on the Metabolism of the Streptococci" Winston Harris Tucker, "Studies on *Clostridium putrificum* and *Clostridium putrefaciens*" Margaret Jane Pittman, "The Pathogenesis of Experimental Pneumococcus Pneumonia" Denis Raymond Augustine Wharton, "Immunological Studies with Tape-worm Antigens"

Cincinnati Ethyl Linna Hopphan, "The Study of Dermal Reactions in the Selection of Bacterial Antigens in Biological Therapy"

Colorado Phillips Thygeson, "The Bacteriology of Trachoma"

Columbia Ada Ranney Clark, "The Role of Clasmatocytes"

Cornell Gustave Ivar Steffen, "The Gaseous Metabolism of *B. tetani*" Alexander Zeissig, "A Study of the Complement Fixation Test in the Detection of Acid-Fast Infections of Cattle"

Harvard John Franklin Enders, "A Study in Bacterial Allergy"

Iowa State College Irl Donaker Wilson, "A Study of Bovine Coccidiosis"

Johns Hopkins Shao-Chung Cheng, "Leucocyte Counts in Rabbits Observations on the Influence of Various Physiological Factors and Pathological Conditions" Raymond Erl Gardner, "Immunity to Transplantable Rat Tumors with Chicken Blood and Vaccine Virus" Wendell Daniel Gingrich "Superinfection and Cross-Immunity in Bird Malaria" Kitty H S Kempner, "The Influence of Diet upon the Susceptibility of the Rat to an Implanted Sarcoma" Lucile Russell Anderson, "A Study of Bacilli of the Genus *Hemophilus* with Regard to the X and V Growth Factors Under Aerobic and Anaerobic Conditions" Cornelius Alfred Perry, "Bacteriological Analysis of Oysters with Special Reference to the Coli-Aerogenes Group as an Indicator of Fecal Pollution" Marvin Mayer Harris, "A Study of the Bacteriology of Decomposing Crabs and Crab Meat" Minnie Behm Kraemer Harris, "A Study of Spirochetes in Chickens with Special Reference to Those of the Intestinal Tract"

Kansas Lucy S Heathman, "Studies of the Antigenic Properties of Some Free Living and Pathogenic Amoebas"

Minnesota Albert Valentine Stoesser, "Further Studies Concerning the Toxin-Antitoxin Union" Newell Richard Ziegler, "A Comparison of Quantitative Methods for the Determination of Bacterial Populations" Paul Henry Guttman, "Addison's Disease A Study of the Pathology and a Statistical Analysis" Albert Ernest Kumpf, "A Study of the Blood Proteins and Lipoids with Special Reference to the Changes Occurring in Renal Diseases"

Pennsylvania M Gwendolyn Hunsicker Mason, "Tissue Culture Studies Showing the Effect of Diphtheria Toxin, Toxoid, and Toxin-Antitoxin Mixture upon Fibroblasts of Chick Embryo Hearts"

Princeton Ernest Wesley Blanchard, "An Experimental Study of the Oposoms of the Blood"

Radcliffe Eva Elizabeth Jones, "Size as a Species Characteristic in *Coccidia* Variation Under Diverse Conditions of Infection"

Western Reserve Robert Allan Moore, "The Total Number of Glomeruli in the Kidney of Man and Animals" Henry Welch, "Studies in Ultra Violet Light"

Wisconsin Rudolph Joseph Allgeier, "Studies in Fermentation" Franklin Ludwig Schacht, "The Hemolytic Streptococcus Content of Milk with Special Reference to the Alpha Type and Mastitis"

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

STUDIES ON THE MECHANISM OF WATER EXCHANGE IN THE ANIMAL ORGANISM
F P UNDERHILL, R KAPSINOW and M E FISK, *Am J Physiol* **95** 302,
315, 325, 330, 334, 339, 348, 1930

In this series of articles there are reported the results of studies of the effect of burns on the animal organism. With superficial burns of the rabbit, there was rapidly produced a marked local subcutaneous edema, which reached its peak in twenty-four hours and did not disappear until the end of the fifth or sixth day. This was accompanied by a marked increase in blood concentration, amounting at times, with a superficial burn of one sixth of the total body surface, to 70 per cent of the total blood volume, and probably to an even greater amount with more extensive superficial burns. The permeability of the local capillaries was greatly affected, as indicated by the passage of dyes into the edematous fluid. The reabsorption of the fluid was slow, after a brief latent period, and substances passing rather freely into the fluid showed little evidence of reabsorption, so that the increased permeability did not operate in both directions. The edematous fluid was practically blood plasma, in both the fluid and the blood serum there was a marked decrease of globulin, which can be explained apparently only as the result of the mechanism of the production of edema, and which may account for the difficulty of water retention in these circumstances. There were, however, certain marked differences in the composition of the edema fluid and the blood serum, the former showing considerably increased amounts of nonprotein nitrogen, potassium, magnesium and inorganic phosphates. Diminution of chloride content in the serum was not observed as long as blood concentration was maintained within normal limits, but this was reduced when the concentration was maintained at a high level. The loss of substance to the edematous fluid did not affect the composition of the tissues with respect to water, ash and chloride content, indicating an apparent conservation of these. Throughout the entire area of the skin there was a great increase of chloride content and of total ash, without, as a rule, any general augmentation of water content. While the accumulation of water in the injured area was dependent on the type of injury, this was not true of the chlorides, which were always greatly increased. The writers infer that the chlorides play a prominent part in the interchange between the blood and the injured tissue. In the case of burned skin, this local increase of chlorides persisted as long as three days, with burned muscle, considerably longer. It was found that with superficial burning, heat might penetrate into the interior cavities enough to raise the temperature appreciably, and so to induce vascular changes apparently sufficient to account for the ulcers, internal hemorrhages, etc. associated with severe burning. Little change of general body temperature was observed, and a rise after twenty-four hours appeared to be due to secondary infection. In animals in which especially severe dehydration was achieved by various methods, it was found that as a result of water deprivation or increased osmotic tension, the body tissues would lose their essential water, with death as an invariable consequence.

H E EGGERS

THE INDUCTION OF THE PSEUDO-PREGNANCY VAGINAL REACTION IN SPAYED MICE BY THE INJECTION OF HUMAN BLOOD C F FLUHMAN, *Am J Physiol* **95** 422, 1930

The reaction of the vaginal mucosa of adult spayed white mice after the injection of blood serum was studied with a view to determining the suitability of the test for human diagnostic purposes. It was found that in such mice there was a

mucification of the vaginal mucosa when they were given injections of serum from patients in whom there was known to be a histologic corpus luteum, during pregnancy, early in the puerperium, during the premenstrual stage and accompanying a corpus luteum cyst. However, the same reaction has been observed with blood specimens from the male with one woman after a bilateral oophorectomy and in four women past the climacteric so that its clinical usefulness would seem improbable.

H E EGGERS

FURTHER OBSERVATIONS ON THE FUNCTION OF THE GALLBLADDER. A G REWBRIDGL, M T HANKE and B HALPERT, *Am J Physiol* **95** 511, 1930

A study of the relative times of disappearance of intravenously administered methylene blue from the liver and the gallbladder of dogs showed that it appeared in the bile within thirty minutes, and reached its highest concentration there in one or two hours. It ceased to be present in the bile from the liver about the thirty-sixth hour following its administration, it usually vanished from the contents of the gallbladder from six to twenty-four hours after the cessation of its discharge from the liver. After oral administration, it disappeared in the bile from the liver at about the thirtieth hour, and from the gallbladder some time between the thirtieth and forty-eighth hour after ingestion. It is concluded that exchange of the content of the gallbladder occurs within about twenty-four hours, but this process is retarded when feeding is unsatisfactory.

H E EGGERS

EXPERIMENTAL ARTERIOSCLEROSIS IN THE RAT. M SWEENEY and E SMITH, *Am J Physiol* **95** 620, 1930

Attempts to induce arteriosclerosis in white rats by means of a diet high in salt, and by constant intensive infection over a period of seven months produced by weekly injections of *Staphylococcus aureus* were unsuccessful. Definite arteriosclerosis, however, was caused by the feeding of approximately 50 cc of viosterol over a period of twenty-five days.

H E EGGERS

COMPLETE TRANSECTIONS OF THE SPINAL CORD AT DIFFERENT LEVELS. C P RICHTER and M B SHAW, *Arch Neurol & Psychiat* **24** 1107, 1930

The spinal cord was cut by Richter and Shaw in twenty-four cats to study the effects on the sweat glands. The levels of section of the cord extended from the sixth cervical to the fifth lumbar segment. Total sections severed the pathways of the sympathetic nerves to the sweat glands causing a temporary increase in the resistance of the skin of from 20,000 to 25,000,000 ohms. After from twenty-five to seventy-five days, the resistance curve resumed the initial low level. The effects of the transection differed from those caused by sympathectomy—the former producing a temporary disappearance of the galvanic skin reflex, the latter causing its permanent disappearance. By measuring the conductivity of the skin, the authors believe that it is possible to contrast the effects produced on the sweat glands by a transected cord, sympathectomy and total section of the nerve “and in this way to throw more light on the question of what central and peripheral factors are involved in the control of the sweat glands.”

GEORGE B HASSIN

EFFECT OF ACUTE EXPERIMENTAL CHOLECYSTITIS ON THE EMPTYING TIME OF THE GALLBLADDER. G T MURPHY, *Arch Surg* **21** 300, 1930

Acute inflammatory processes in the gallbladder were produced experimentally by the intravenous injection of eusol into dogs. In ten experiments only one instance was encountered in which the acutely inflamed gallbladder showed any evidence of emptying in response to a fat meal.

N ENZER

AMYOTONIA CONGENITA (OPPENHEIM'S DISEASE) IN IDENTICAL TWINS W D FORBUS and F S WOLF, Bull Johns Hopkins Hosp 47 309, 1930

In the absence of any satisfactory understanding of the origin of these cases of amyotonia congenita as well as of those we have found in the literature, our inclination is naturally to place the greater emphasis on that explanation of the lesions to which there appear the smallest number of objections, and that explanation seems to be the one based on some injury to the developing embryo which localizes especially in the anterior horn of the gray matter of the spinal cord, the condition of the muscles being secondary to this injury. When viewed in this way, amyotonia congenita comes to fall obviously outside of the group of true myopathies

AUTHORS' SUMMARY

THE PATHOGENESIS OF THE FORMS OF JAUNDICE ARNOLD RICE RICH, Bull Johns Hopkins Hosp 47 338, 1930

In this paper the various forms of jaundice are considered in the light of our present information regarding the physiology and pathology of the formation and excretion of bile pigment. It is pointed out that, from the standpoint of the clinical and pathologic evidence, cases of jaundice are separable, on the basis of pathogenesis, into two main types. The first type, retention jaundice, results from an overproduction of bile pigment, usually associated with conditions (anoxemia, fever, immaturity) which tend to render the excretory power of the liver subnormal, enough bilirubin is therefore retained in the blood to stain the tissues. This form of jaundice is characterized clinically by indirect-reacting plasma bilirubin, increased amounts of fecal urobilin and urobilinuria. Pathologically, the ducts are patent, but the hepatic cells may show atrophy or cloudy swelling, depending on the associated condition of which the jaundice is a symptom. The second type, regurgitation jaundice, is caused by the reflux of whole bile from the canaliculi into the blood stream. This type is characterized clinically by direct-reacting plasma bilirubin, subnormal amounts of fecal urobilin and the presence of bilirubin and bile salts in the urine. The pathologic basis of this form of jaundice is rupture of the canaliculi resulting from obstruction of the ducts or from necrosis of the hepatic cells. Combined forms may occur, as well as a transition from one of these types of jaundice to the other. A classification is offered in which the two types (retention jaundice and regurgitation jaundice) are further subdivided from the standpoint of etiology and pathogenesis, and the reasons for the various subdivisions are discussed.

AUTHOR'S SUMMARY

THE PRODUCTION OF ACUTE NEPHRITIS BY MEANS OF A PNEUMOCOCCAL AUTOLYSATE S S BLACKMAN, J H BROWN and G RAKE, Bull Johns Hopkins Hosp 48 74, 1931

Characteristic acute and subacute nephritis has been produced in rabbits by means of an autolysate prepared from type I pneumococcus and also by means of intradermal infection with virulent strains of pneumococci. The toxin affects the glomerular capillaries, as evidenced by the hyaline and fibrin thrombi and by the blood and fibrin in the tubules, and produces injury and necrosis in the epithelium of the tubules and glomeruli. In a certain number of cases the damage to the kidneys has been associated with marked edema of the tissues and with ascites.

AUTHORS' SUMMARY

EXPERIMENTAL AIR EMBOLISM OF CORONARY ARTERIES G RUKSTINAT, J A M A 96 26, 1931

Dogs whose coronary arteries are plugged with air die promptly. In such animals and also in human beings dying of air embolism, there are no lesions demonstrable anywhere to explain death unless an exception is made of the presence of air in the blood. In air embolism of the coronary arteries, either

recovery or death takes place promptly. Direct cerebral air embolism through the carotid arteries is succeeded by cerebral irritation which does not develop in dogs with solely coronary air embolism, although both may have apparently similar amounts of air in their leptomeningeal vessels. Delayed cerebral air embolism was not observed in dogs recovering from coronary artery air embolism.

AUTHOR'S SUMMARY

THE ANTIRACHITIC ACTION OF COD LIVER OIL AND IRRADIATED ERGOSTEROL
A. M. PAPPENHIMER, J. Exper. Med. **52** 805, 1930

Cod liver oil and viosterol in therapeutic doses are antirachitic in rats in the absence of the parathyroid gland, or of the thymus, or of both.

AUTHOR'S SUMMARY

MOUSE LEUKEMIA. M. N. RICHIER and E. C. MACDOWELL, J. Exper. Med. **52** 823, 1930

Several lines of lymphatic leukemia in mice, experimentally transmitted by inoculation into hosts of a closely inbred strain, have been established and carried on simultaneously. Among the inoculated mice there were found different types of response, according to the line of leukemia inoculated. The differences consisted mainly in the extent or distribution of lesions. Although the same line did not always show the same distribution of lesions, there was a distinct tendency for the cases in a line to present the same characteristics on successive transfers over a considerable period. The lesions characteristic of a line were not necessarily those present in the spontaneous case from which the first transfer of the line was made. As the mice used for inoculation were genetically uniform, the differences between the lines are not due to genetic differences in the hosts, but to differences in the materials inoculated.

AUTHORS' SUMMARY

THE RELATIVE REACTION WITHIN LIVING MAMMALIAN TISSUES. H. P. GILDING, J. Exper. Med. **52** 949 and 953, 1930

The distribution and segregation of highly colloidal vital dyes follow definite lines irrespective of the pigment employed, the localization of one dye differing from that of another only in details. Erythrolitmin well exemplifies this rule. The minutiae of the staining here reported are not unique, nor indeed are they peculiar to extraneous pigments. The granular localization in cardiac muscle resembles that seen in brown atrophy of the heart, while the general distribution of erythrolitmin has similarities to that of the pigments present in clinical and experimental hemochromatosis. There is reason to suppose that the abundance of pigment in the parenchyma of the liver in this disease is the result of hepatic damage. Taken together, the facts give ground for the supposition that the morbid pigments just mentioned are segregated within the body by the same processes as are the highly colloidal "acid" dyes, a view already put forward by von Mollendorff.

By a variety of methods, necrosis of individual cells was produced in the living animal. The death of the cells was found to be clearly perceptible by means of the changes in the color of segregated erythrolitmin at a time when it was not yet recognizable by ordinary histologic methods. The hue of the dye pointed to an alteration in the direction of alkalinity, but the extent of this could not be determined owing to the limited range of the indicator. Cartilage damaged by freezing *in situ* becomes alkaline, its reaction now approximating that of the blood. The observations support the view that within the body the autolysis of individual cells and of small tissue masses may take place under conditions of slight alkalinity.

AUTHOR'S SUMMARIES

EXPERIMENTAL ELECTRIC SHOCK R W I URQUHART and E CLARK NOBLE,
J Indust Hyg **11** 154, 1929

When an alternating current of definite strength is passed directly through the base of the brain for a certain period of time, a condition of profound paralysis or block becomes established in the nerve centers. The presence of this block was demonstrated by experiments in which reflex effects normally functioning through these centers (respiratory, vagal, conjunctival) were found to be absent following the shock. It was further shown that, after a certain interval following break of the electric current, the paralysis or block is recovered from and the reflexes return, provided efficient artificial respiration is meanwhile applied, and provided there has been no charring of nerve structures. The institution of therapeutic means during this period of block (such as inhalation of air and oxygen mixtures, oxygen, carbon dioxide or intravenous injection of epinephrine) were of no avail, the application of efficient artificial respiration being the only factor responsible for shortening the block period.

An alternating current causes a similar condition of block in the centers of the lower portion of the spinal cord in decerebrated cats. This condition is manifested by the abolition of those reflexes that are dependent on the conductivity of that portion of the cord through which the current has passed. It was also found that following the passage of a relatively strong current through a nerve, a degree of block is established from which the nerve does not recover in a reasonable length of time.

C G WARNER

THE MECHANISM OF OBSTRUCTIVE PULMONARY ATELECTASIS C M VAN
ALIEN and W E ADAMS, Surg Gynec Obst **50** 385, 1930

Quiet or suppressed respiration with bronchial obstruction does not lead to pulmonary atelectasis in the normal lung.

Straining respiration is essential to the production of obstructive pulmonary atelectasis in the normal lung.

Valvular obstruction produces atelectasis much more rapidly than does total obstruction, but there is no evidence that valvular obstruction occurs spontaneously in man.

Pent up bronchial air is probably lost from the lung by absorption by the blood stream.

Obstructive atelectasis develops centrifugally through the parenchyma of the lung.

Decreased intrapleural and intrabronchial pressures occur characteristically in obstructive pulmonary atelectasis.

AUTHORS' SUMMARY

MICRO-INJECTION STUDIES OF CAPILLARY BLOOD PRESSURE IN HUMAN SKIN
EUGENE M LANDIS, Heart **15** 209, 1930

The micro-injection method for directly determining mean blood pressure in single capillaries has been modified to suit the skin at the base of the human finger-nail. Average blood pressure in the arteriolar limb is 32 mm of mercury, at the end of the loop, 20 mm, and in the venous limb, 12 mm. The fall of blood pressure does not cease at the junction of the arterioles and capillaries but continues unbroken through the capillary loop. Average blood pressure in the arteriolar limb is above, and in the venous limb below, the osmotic pressure of the plasma proteins. These direct pressure readings in human capillaries are in agreement with Starling's hypothesis of fluid balance. When the hand is placed at various levels above the suprasternal notch, the arteriolar and venous capillary pressures remain almost constant, but with the hand below the suprasternal notch they increase by the increment of hydrostatic pressure. Venous congestion by a pneumatic cuff produces a rapid rise of capillary pressure, which reaches cuff pressure within from fifteen to forty-five seconds. Capillary pressure finally

exceeds cuff pressure by from 8 to 14 mm of mercury. Hyperemia of the skin at the base of the nail due to heat is accompanied by a rise of capillary pressure to as much as 60 mm of mercury in the arteriolar limb and to as much as 45 mm in the venous limb of the capillary. In the histamine flare, arteriolar capillary pressure rises to between 32 and 50 mm of mercury, and venous capillary pressure to between 27 and 39 mm. Local cooling of the skin produces first a fall in capillary pressure of from 6 to 11 mm of mercury, and after five to eight minutes a secondary rise of from 2 to 14 mm above the original normal pressure. When the skin is whealed by freezing, average capillary pressure rises to 49 mm of mercury in the arteriolar limb and to 32 mm in the venous limb. In the blister, average arteriolar capillary pressure is 41 mm of mercury, and average venous capillary pressure 23 mm of mercury. The direct micro-injection method is compared, from the point of view of its accuracy, to certain direct and indirect methods. The observations are discussed with reference to the mechanism of fluid balance under average conditions and during hyperemia.

AUTHOR'S SUMMARY

RELATION OF THE PREEN GLAND (GLANDULA UROPYGIALIS) OF BIRDS TO RICKETS. H. C. HOU, Chinese J. Physiol. **3** 171, 1929

Removal of the preen glands from adult birds produces in some (fowl and duck) a marked disturbance of the plumage and an impairment of general health and in others (pigeons) only a slight disturbance of the plumage. Removal of the preen glands from young rachitic or normal fowls produces permanent rickets in spite of subsequent normal feeding, environment and sunshine. Occlusion of the opening of the preen glands of ducks causes some disturbance of plumage and loss of weight. The possible relationship between the sebaceous secretion and the formation of the antirachitic vitamin is discussed.

TESTICULAR GRAFTS. M. GIANOTTI and G. BERTINI, Arch. ital. di anat. e istol. pat. **1** 797, 1930

Homoplastic grafting of testicular tissue was carried out subcutaneously, preperitoneally and in the tunica vaginalis of guinea-pigs and dogs. After from five to forty-five days, necrosis of the testicular tissue took place. After the first week, connective tissue proliferation and active exudation were observed in the surrounding tissue, without a cellular proliferation in the seminiferous epithelium or in the intertubular connective tissue.

E. WEISS

THE RELATION OF THE HORMONE OF THE ANTERIOR LOBE OF THE HYPOPHYSIS TO THE TESTIS. M. BORST, Deutsche med. Wchnschr. **56** 1117, 1930

This hormone injected into young mice less than 26 days old stimulates the growth and division of the cells of the germinal epithelium. The interstitial tissue of the testis also proliferates, and the seminal vesicles and prostate gland increase in size much more rapidly than in untreated control animals. In mice older than 26 days, the germinal epithelium does not react so readily, and large doses produce degenerative changes. The prostate gland and seminal vesicles, however, increase rapidly in size as in younger mice, and the interstitial tissue of the testes also proliferates markedly.

PAUL BRESLICH

THE EFFECT OF HYPOPHYSIS HORMONE ON YOUNG MALE RATS. H. BALTERS, Deutsche med. Wchnschr. **56** 1382, 1930

Hormone from the anterior lobe of the hypophysis stimulates the differentiation of the infantile cell elements lining the tubules of the testes of young rats to spermatogonia and spermatocytes. In more mature animals the stimulation is less marked, and large doses of the hormone cause degenerative changes of the

germinal epithelium The hormone also causes a marked proliferation of the interstitial tissue of the testis and stimulates the growth of the prostate gland and seminal vesicles which are distinctly larger than these tissues in untreated control animals

PAUL BRESLICH

EXCESSIVE USE OF TOBACCO AND CORONARY SCLEROSIS K PIENGE, *Deutsche med Wchnschr* **56** 1947, 1930

The postmortem examination of two men, 46 and 40 years old, who had died suddenly, disclosed marked sclerosis of the coronary arteries in one, and a recent coronary thrombosis in the other In each instance, the aorta and its main branches were practically unchanged Both men had smoked tobacco excessively Microscopically, there were regions of necrosis and sclerosis of the media of the coronary arteries that resembled the changes produced experimentally in animals by chronic nicotine poisoning Nicotine is said to cause a spasm of the coronary arteries which eventually results in anatomic changes

PAUL BRESLICH

ALIMENTARY CHOLESTEREMIA AND BLOOD SUGAR IN DIABETES E SORKIN and M BATUSCHANSKAJA, *Ztschr f d ges exper Med* **74** 138, 1930

Diabetic hypercholesteremia is not dependent on the blood sugar, during fasting, but is directly related to the degree of acidosis By feeding olive oil, the blood sugar may be lowered and the blood cholesterol raised Similar changes may occur in persons with diabetes without feeding fat In the first instance, the source of the increased cholesterol in the blood is exogenous, in the second instance, endogenous The lowering of the blood sugar may be due to the checking influence of fat on the thyroid gland

PEARL ZEEK

EXERCISE AND SWEAT GLANDS A N KRESTOWNIKOFF, *Ztschr f d ges exper Med* **74** 200, 1930

Observations made on runners showed that the more lactic acid excreted in sweat, the less albumin appeared in the urine The suggestion is made that the sweat glands may protect the kidney tissue from the action of lactic acid

PEARL ZEEK

THE EFFECT OF VITAMIN D AND PARATHYROID HORMONE ON THE STORAGE OF CALCIUM FERDINAND HOFF and ERNST HOMANN, *Ztschr f d ges exper Med* **74** 258, 1930

Following the injection of 50 units of parathyroid hormone (parathormone) in cases of tetany, a biphasic reaction occurred at first there was a rise in the blood calcium, a decrease in the alkali reserve and a lessening of the potassium-calcium quotient, a leukocytosis with myeloid tendencies occurred and sensitivity to electrical stimulation was decreased, the symptoms of tetany disappeared In the second phase, there was a disappearance of all these vegetative regulatory phenomena in reverse order Parathyroid hormone and vitamin D are apparently antagonistic in their action in some respects But experiments showed that visceral calcification following the administration of vitamin D was not lessened but actually increased by the simultaneous administration of parathyroid hormone At the same time there was decalcification of skeletal bone, at times so great as to lead to spontaneous fractures

PEARL ZEEK

THE DEPOSITION OF VITAL DYES IN THE LYMPH NODES S SAWELSOHN, *Ztschr f d ges exper Med* **74** 607, 1930

Subcutaneously injected trypan blue and india ink are subsequently held partly by the subcutaneous tissues and partly by the regional lymph nodes If a dye concentration of 1:10,000 is used the deposition is in the histiocytes of the con-

nective tissues at the injection site, none being found in the regional lymph nodes two days after injection. If a concentration of 1:1,000 is used, the dye appears also within the lymph nodes. A concentration of 1:100 causes, in the same time interval, a deposition of dye in the reticulo-endothelium of the internal organs. Blocking of the lymph nodes with india ink several days previously, apparently has no effect on the fate of subsequent injections of trypan blue. Venous hyperemia in the extremity chosen for subsequent injections of dyes does not prevent deposition, either local or at distant sites, but complete blockage of the venous circulation is a real hindrance to the deposition of the dye in the regional lymph nodes and prevents its deposition in the internal organs.

PEARL ZECK

THE EFFECT OF TUBERCULOUS INFECTION ON METABOLISM. HANS FISCHER and EDWARD FROMMLI, *Ztschr f d ges exper Med* **74** 646, 1930

In experimentally produced acute miliary tuberculosis, there occurs, during the incubation period, a definite increase in the consumption of oxygen, which cannot be attributed to fever. Likewise, during the manifest stage of the disease, the increased metabolism does not run parallel to the temperature. Various explanations are offered for this phenomenon.

PEARL ZECK

DEGENERATION OF THE TUBER CINLREUM AS A FACTOR IN THE DESTRUCTION OF THE CELLS OF THE UPPER SYMPATHETIC GANGLION. G. IWANOW, *Ztschr f d ges exper Med* **74** 773, 1930

Experimental injury to the tuber cinereum was followed by degenerative changes in the superior cervical ganglion, beginning usually as a chromatolysis and homogeneous appearance of cytoplasm and nucleus, then a change in shape of the nucleus and finally complete disappearance of the nucleus. Changes were observed also in the neurofibrils.

PEARL ZECK

Pathologic Anatomy

SYPHILIS OF THE AORTA AND HEART. H. S. MARTLAND, *Am Heart J* **6** 1, 1930

From a clinical and pathologic standpoint, I believe that we should regard syphilis of the aorta and heart as an acquired disease (congenital cases being infrequent) developing insidiously and showing symptoms years after the initial infection. It is possible to recognize clinically and to diagnose early aortitis, aortic regurgitation, narrowing of the coronary ostia, aneurysm or any combination of these lesions. Treatment and prognosis should be based mainly on such recognition. The myocardium in syphilis is frequently normal. When the aortic valve is involved, the main myocardial lesion is hypertrophy. Atrophy due to manition is occasionally encountered. Specific lesions of the myocardium are infrequent and, when they occur, are so slight in extent as to be of little practical importance. It is safer and better to assume that the coronaries distal to the aortic wall are usually normal in pure, uncomplicated syphilis, and that coronary occlusions, anemic infarcts, necrosis of heart muscle, replacement fibrosis, aneurysms of ventricular walls and fibrous myocarditis are almost entirely due to coronary injury dependent on an arteriosclerotic process and have nothing to do with syphilis. That rheumatism and other infections may also produce forms of interstitial myocarditis is obvious. It appears that syphilis does not play an important role in the production of such lesions.

AUTHOR'S SUMMARY

THE GROSS PATHOLOGY OF THE HEART IN CARDIOVASCULAR SYPHILIS. JAMES G. CARR, *Am Heart J* **6** 30, 1930

Except for the predominant hypertrophy of the left ventricle, which resembles that of essential hypertension, the gross myocardial changes associated with syphilitic aortitis are not characteristic. The incidence of myocardial degeneration as a

result of syphilitic involvement of the coronary circuit is not great. The frequent occurrence of arteriosclerosis with syphilitic disease makes it difficult to separate these two factors as causes of coronary disease. Probably less than 10 per cent of the cases with aortic syphilis are associated with syphilitic coronary disease. In this series, involvement of the coronary orifices in the typical wrinkling of syphilitic aortitis was found only ten times, an incidence of 8.4 per cent. Aortic insufficiency is found in about 20 per cent of the hearts associated with syphilitic aortitis. It is the lesion most easily recognized and is most likely to be present in the advanced cases. In this series, it occurred in 19, or 37.2 per cent, of the hearts weighing over 450 Gm. Hypertrophy of the heart is a significant index of the degree of cardiac involvement in cardiovascular syphilis. This sign is absent in the latent stage of the disease, but becomes increasingly important as signs of cardiac disease appear. In a group of forty-four persons in whom autopsy showed definite cardiac enlargement of various degrees up to a maximum of 50 per cent, twenty-one died of intercurrent disease, and fifteen of these had not had a diagnosis of cardiac disease. Some of these presented symptoms of acute disease so marked as to cloud the picture but others did not. Both aortic regurgitation and hypertension were infrequent in this group. The presence of an unexplained or "idiopathic" cardiac hypertrophy in persons of middle life may well excite the suspicion of syphilis. The two important causes of cardiac hypertrophy are aortic regurgitation and hypertension, the latter of which is a common occurrence in this type of case. There is a significant incidence of contracted kidney with advanced stages of cardiovascular syphilis. In this series, aneurysm was found more frequently in the cases characterized by relatively minor cardiac symptoms. These results seem to illustrate the frequency with which aneurysm may be present without involving the heart or causing symptoms of cardiac disease.

AUTHOR'S SUMMARY

THE LOCALIZATION OF THE LUETIC VIRUS IN THE AORTA J. W. McMEANS, Am Heart J 6 42, 1930

It is our belief that in syphilitic aortitis the intima is involved primarily by direct infection from the blood stream. It may also be involved from the adventitia through the vasa vasorum. Histologically, the lesions are the same. Undoubtedly, the most serious lesions produced by syphilis in the aorta and heart are those of syphilitic aortic endocarditis with regurgitation and occlusion of the coronary orifices. This is intimal disease. Therefore, it would appear that syphilitic intimal disease of the aorta is more important clinically than syphilitic medial disease.

AUTHOR'S SUMMARY

HYPERPLASIA OF THE CORPUS ADIPOSUM BUCCAE (SUCKING PAD) FRANK C. NEFF and JOHN A. BILLINGSLEY, Am J Dis Child 40 813, 1930

We have been able to find the record of a unilateral hyperplasia of the corpus adiposum malae in a 15 year old boy and a few cases of lipoma limited to one side in children past infancy. We have been unable to learn of any report in which mention is made of bilateral pathologic enlargement confined to the corpus adiposum buccae in the newly born child. Scammon, as a result of his research on the development and fine structure of the sucking pads, found that at birth the pad is a structure particularly prominent in the well nourished child. In fetal life the growth in the first five months is principally due to increase in the number of fat lobules. In the later fetal months, the fat body grows because of the forming of new fat cells and the increase in size of the individual fat cells. Scammon stated that new fat cells stop forming usually by the end of the seventh fetal month, occasionally not until the last month. In the case here reported the infant was not robust at first, but was small and premature and possibly was affected by the toxic state of the parturient mother. The cheeks were not wasted. It is possible that the fat pads continued to grow for the first ten or twelve days after birth, and at a rapid rate after feeding and the normal influences of growth were established. As a more

plausible explanation, the finding of a mild inflammatory reaction in the biopsy material and the subsequent rather rapid decrease in the size of the remaining fat pad would suggest that the enlargement of these bodies may have been hyperplastic, due to a toxic influence

AUTHORS' SUMMARY

MEDIASTINAL TERATOMA IN AN INFANT HERBERT B WILCOX and MARTHA WOLLSTEIN, *Am J Dis Child* **41** 89, 1931

A solid mediastinal teratoma occurring in a male infant, aged 6 months, and giving symptoms over a period of three months, is described, with the microscopic content of tissues from the three embryonal layers

AUTHORS' SUMMARY

SUBACUTE BACTERIAL ENDARTERITIS OF PULMONARY ARTERY ASSOCIATED WITH PATENT DUCTUS ARTERIOSUS AND PULMONIC STENOSIS HARRY GORDON and DAVID PERLA, *Am J Dis Child* **41** 98, 1931

An instance is reported of subacute bacterial endarteritis (*Streptococcus viridans*) of the pulmonary artery associated with a patent ductus arteriosus and congenital pulmonary stenosis. None of the valves was involved. The relationship of congenital defect to bacterial inflammation is discussed

AUTHORS' SUMMARY

JUVENILE EMBOLIC GANGRENE OF AN UPPER EXTREMITY JOHN DORSEY CRAIG and WALDEN E MUNS, *Am J Dis Child* **41** 126, 1931

A case of aortic stenosis of rheumatic origin with an accompanying embolic gangrene of the right hand in a child is here reported because of its clinical interest and rarity

AUTHORS' SUMMARY

TUBULAR NEPHRITIS (NEPHROSIS) S BURT WOIBACH and KENNETH D BLACKFAN, *Am J M Sc* **180** 453, 1930

We believe that the eight cases here presented, because of the clinical and pathologic features common to them all, are representative of a disease entity in childhood. This belief implies a common etiology or pathogenesis for the series. The pathologic changes in the kidneys afford no premises for the explanation of the important physiologic disturbances, and therefore we do not believe that the primary effect of the etiologic agent is on the kidneys or that the important manifestations of the disease are consequences of injury specific to the kidneys. The histologically demonstrable damage to the kidneys was found in the tubules. The glomeruli showed only lesions accountable for either by the terminal infection or severe degeneration of the tubules of the same units. In general, the glomeruli were without lesions. A conclusion regarding the role of the thyroid gland in this disease is not possible. The lesion in the thyroid gland is probably a manifestation of functional exhaustion and therefore probably is neither cause nor direct consequence of the damage to the kidney. The pathologic changes in the liver, slight atrophy and degeneration of the hepatic cells, may also be interpreted as effects of overtaxed functional activity consequent to the loss of proteins from the blood. While offering no substitute, we believe that any name implying a renal origin, such as nephrosis or tubular nephritis, is not appropriate to this disease

AUTHORS' SUMMARY

MITOSIS IN MYELOBLASTS IN PERIPHERAL BLOOD WILLIAM A GROUT, *Am J M Sc* **180** 607, 1930

Photomicrographs of a series of leukoblastic cells in mitotic division are shown. These cells from the circulating blood of a patient with acute myeloblastic leukemia form a complete series of mitotic figures from early prophase through metaphase

and anaphase to latest telephase. The angle that the chromosomes bear to the spindle can be measured approximately in these photomicrographs and is found to be close to 70 degrees, agreeing with the goniometric measurements made by Ellermann of myeloblasts in tissue sections. Mitotic division in leukemic cells in peripheral blood is added evidence of a possible relationship between leukemia and malignant growth.

AUTHOR'S SUMMARY

ACUTE INTERSTITIAL PANCREATITIS IN TWO CASES OF DIABETIC COMA ALVIN G. FOORD and BYRON D. BOWEN, *Am J M Sc* **180** 676, 1930

Two fatal fulminating cases of diabetic coma in young adults have been reported with the observations at necropsy. The chief pathologic change in each of these cases was acute diffuse interstitial pancreatitis, which was probably a factor in the precipitation of coma. Examination of the literature shows only one similar case (Warren) and another (Gibb and Logan) associated with an infected hand. In our two cases no source of the infection could be determined. In one of our cases there was histologic evidence of a high degree of disturbance in lipid metabolism as manifested by a huge liver that showed extreme fatty metamorphosis, by the deposit of lipid substance in the abdominal lymph nodes, spleen and kidney, and by lipemia. It is extremely probable that in this case the diabetes had not been fully under control for some time, as the patient had not previously seen a physician in about three years and was an unmanageable patient, as we know from past experience with him.

AUTHORS' SUMMARY

GASTRIC HEMORRHAGE DUE TO FAMILIAL TELANGIECTASIS L. NAPOLEON BOSTON, *Am J M Sc* **180** 798, 1930

Familial telangiectasis is the etiologic factor in a definite class of hemorrhages, which take place in the presence of normal physiologic responses by both the capillary and the venous blood. Recurrent gastric hemorrhages were experienced during early life by each of the three patients whose cases were studied, and attacks of hemorrhage were often accompanied by brief periods of syncope. Judged by the small number of reports of cases, familial telangiectasis does not shorten the span of life or inhibit development. Familial gastric hemorrhage has been observed in persons who have also experienced recurrent attacks of hemorrhage from other mucous surfaces. The vascular defects common to the familial condition characterized by hemorrhages from the mucous membranes are to be found among other members of the same family and in their near relatives. The tendency to familial hemorrhage is transmitted by both the maternal and the paternal parent to the offspring.

AUTHOR'S SUMMARY

TROPICAL SPRUE ITS DIFFERENTIATION FROM PERNICIOUS ANEMIA BY THE ARNETH COUNT JAMES D. TYNER, *Am J Trop Med* **10** 435, 1930

The average Arneth index of ten cases of pernicious anemia was 32.45. The average Arneth index of seventeen of twenty cases of tropical sprue was about normal, or 62.1. The Arneth count may be of aid in the differential diagnosis of tropical sprue and pernicious anemia.

AUTHOR'S SUMMARY

LEUKEMIC CHANGES OF THE GASTRO-INTESTINAL TRACT W. SCLAIR BOIKAN, *Arch Int Med* **47** 42, 1931

Fourteen cases of leukemia, eleven myelogenous and three lymphatic, were studied with reference to the gastro-intestinal involvement. Nonspecific changes were found in nine cases of acute myelogenous leukemia, consisting of hemorrhages, ulceration and secondary inflammatory processes. In two cases (acute myelogenous leukemia) there were no changes. Specific changes were found in two cases of

acute myelosis, consisting of an infiltration of the appendix and an infiltration of Peyer's patches, respectively. Specific changes were found in one case of chronic lymphatic leukemia the stomach was enormously enlarged, with huge convolutions on the inner surface, giving it a brainlike appearance, and the intestines were beset with plaques and polyp-like infiltrations. In reviewing the literature, no similar case was discovered. The case was found, however, to parallel exactly those described as aleukemic lymphadenosis or pseudoleukemic gastro-intestinalis. From these facts it is concluded that the aleukemic and leukocythemic leukemias are fundamentally identical. In further support of this conclusion, a last case is described in which an aleukemic lymphadenosis terminated as an acute leukocythemic lymphadenosis. The symptoms in leukemia gastro-intestinalis are briefly discussed, and their importance is emphasized.

AUTHOR'S SUMMARY

TUMOR OF THE FILUM TERMINALE E. SACHS, D. K. ROSE and A. KAPLAN,
Arch Neurol & Psychiat **24** 1133, 1930

As only three cases of tumor of the filum terminale are on record (those of Lachman, Gowers and Spiller), the two cases reported here are of interest. In the first case the essential complaints were difficulty in urination followed by acute retention, a "neurogenic" bladder, saddle-like anesthesia (corresponding to the third, fourth and fifth sacral segments of the skin), hyperactive ankle and knee jerks, ankle clonus, a Babinski sign on the left and an Oppenheim sign bilaterally. The pressure of the spinal fluid, which was 90 mm, rose, after bilateral jugular compression for ten seconds, to 170 mm, the result of the Pandy test was 2 plus, otherwise the spinal fluid was normal. Though tumor of the spinal cord was diagnosed, its location could not be determined, even with the injection of iodized poppy seed oil 40 per cent, this dropped to the bottom of the canal. Operation revealed an encapsulated tumor, 4 by 1.5 cm, containing several cysts, attached at one end to the spinal cord with which it was fused and at the other end to a thin fibrous cord. The microscopic diagnosis was hemangio-endothelioma. The patient recovered completely.

In the second case, the initial symptoms were progressive atrophy and weakness in the lower portions of both legs for several years, followed by pain and soreness and dysuria, the ankle jerks were absent, sensory disturbances were present in the areas of the fourth and fifth sacral segments and hypesthesia to pin pricks was detected on the posterior surface of the knee downward to the lower portion of the gastrocnemius muscle. An Oppenheim sign was present on the left and a normal ankle jerk on the right. The rectal sphincter was relaxed. Spinal puncture showed no evidence of block. Operation disclosed a tumor, 3.5 by 2 by 1 cm, of the filum terminale, it weighed 2 Gm (hemangio-endothelioma). Its removal was followed by marked improvement in the bladder and some improvement in the legs. Studies of cases of disease of the filum terminale may help clear up the physiology of micturition, which is not fully understood.

GEORGE B. HASSIN

HYDROCEPHALUS GEORGE B. HASSIN, *Arch Neurol & Psychiat* **24** 1164, 1930

The study of twelve cases of hydrocephalus of so-called communicating type in which the obstruction is elsewhere than in the ventricles, revealed, aside from the distention of the latter by excessive amounts of fluid, also dilatation of the sub-arachnoid spaces, mainly over the convexity of the brain, and of the cerebral tissue spaces. The condition was one of general hydrops involving the brain and the intracerebral (ventricles), as well as the extracerebral (subarachnoid) cavities. In all the cases, the choroid plexuses, which are supposed to produce the excessive amounts of the fluid in hydrocephalus, were atrophied or sclerosed or buried within the ventricular tissue. The pacchionian bodies, which according to the popular conception drain the spinal fluid, were excessively developed and not shrunk as they should have been if they drain the spinal fluid. The perineural spaces along the cranial nerves were infiltrated and some basilar cisterns, especially the chiasmatic,

appeared obliterated by the protruded floor of the third ventricle. In general, there were infiltrations with hematogenous elements, hyperplasia of connective tissue and, in one instance, in an infant, ossification of the dura, in the ventricles, subarachnoid spaces, choroid plexuses, perineural spaces of the cranial nerves, the meninges and the cerebral tissue themselves. Of these the changes in the ventricles, cerebral parenchyma, arachnoid villi and pacchionian bodies were secondary to those in the meninges, the subarachnoid and the perineural spaces of the cranial nerves. The result of the latter changes was interference with the discharge of the cerebrospinal fluid which normally occurs into the ventricles and the subarachnoid spaces from the cerebral tissues by way of the Virchow-Robin spaces. As the choroid plexuses were severely damaged in all the cases, they could not be responsible for the excessive accumulation of the fluids. They are thus not the secretory, but most likely, as other pathologic facts indicate, the excretory, organs. They hold back the harmful products of the tissue fluids, rendering them harmless and absorbable. It also follows that the pacchionian bodies do not serve the purpose of absorption of the cerebrospinal fluid, which is absorbed exclusively by way of the perineural spaces of the cranial nerves.

AUTHOR'S ABSTRACT

SCHILDER'S ENCEPHALITIS PERIAXIALIS DIFFUSA M. M. CANAVAN, Arch Neurol & Psychiat 25 299, 1931

Canavan's patient, a rather poorly nourished child, with a history of nasal discharge and a swollen ear drum was observed continuously from the age of 10 weeks to that of 16½ months, when the child died. The most prominent symptoms were increased size of the head, which suggested hydrocephalus, nystagmus, vomiting and mental deficiency, "it was questionable whether the child saw objects", optic atrophy (beginning) was noticed. At one examination (at the age of 16 months) strabismus and Kernig's sign were present, with increased knee jerks. Necropsy revealed bulging of one hemisphere, a firm cortex (after hardening in a solution of formaldehyde), and pink, soft, retractile white matter "resembling mucoid degeneration" especially in the posterior portion of the brain, the whole cerebellum, though it had been in formaldehyde for almost three months, was soft to the touch. Microscopic examination showed lacy edema, especially of the cerebellum, with traces of glial cells fairly well preserved, absence of fat, traces of which were present only in the walls of the blood vessels, and subcortical loss of myelin. The weight of the brain was 1,890 Gm.

GEORGE B. HASSIN

THE CELLS OF THE SPINAL ARACHNOID IN PATHOLOGIC CONDITIONS I. B. DIAMOND, Arch Neurol & Psychiat 25 373, 1931

Diamond studied the condition of the arachnoid cells, also known as mesothelial cells or membrane cells of Key and Retzius, in tabes, taboparesis, multiple sclerosis, multiple myeloma of the vertebrae, myelomalacia, subacute combined degeneration of the cord, spinal syphilis, streptococcus infection, tetanus, neurinoma, uremia, Pott's disease, carcinoma of the mediastinum, hemiplegia and in normal conditions. The arachnoid at various levels of the spinal cord was gently stripped from the pia, clipped with scissors and stained by various methods, especially the hematoxylin staining method of Ehrlich. In all the cases the arachnoid cells appeared proliferated and often showed mitotic figures and cluster formation. The clusters were present largely on the posterolateral surfaces of the cord and on the posterior roots. Over the anterior aspect of the cord they were less in evidence. Of the pathologic conditions, tabes showed abundant nests, which were also much denser than in other conditions. Contrasting the changes seen in arachnoid cells in tabes with those seen in other conditions, such as subacute combined degeneration of the cord, multiple sclerosis, myelomalacia, etc., Diamond came to the conclusion that they differ somewhat, depending most likely on the spinal fluid. Exposed to the latter, the arachnoid cells react differently according to the sub-

stances in the fluid. As the spinal fluid in tabes differs, for instance, from that in multiple sclerosis the reaction also differs. This is fully borne out by the histologic changes. In general, the cell changes are simple swelling, active proliferation, formation of macrophages, focal hyperplasia with formation of cell clusters, a diffuse infiltration with a tendency to syncytial formation and frequent regressive changes, such as calcification.

GEORGE B. HASSIN

TUBERCLE-LIKE STRUCTURES IN HUMAN GOITERS R. H. JAFFL, Arch Surg **21** 717, 1930

Epithelioid giant cell tubercle-like structures are found occasionally in both diffuse hyperplasia and nodular goiters. They have been considered as tubercles. On the basis of 4 cases in 300 specimens, the author believes that these are not tubercles. No caseation or tubercle bacilli were found in the tissues in these 4 cases, and transformation of follicles into nodules could be demonstrated, while the epithelioid-like cells and giant cells could be traced to the follicular epithelium. The author believes that these pseudotuberculous formations are the result of involutionary changes in old and newly formed follicles.

N. ENZER

COMPLETE OCCLUSION OF THE SUPERIOR VENA CAVA BY PRIMARY CARCINOMA OF THE LUNG A. L. BROWN, Arch Surg **21** 959, 1930

The author gives a report of a case of primary peribronchial carcinoma in a man 65 years of age with complete obstruction of the superior vena cava by compression and subsequent thrombosis.

N. ENZER

CONGENITAL SYPHILIS OF ADRENAL G. L. FITE, Bull. Johns Hopkins Hosp **48** 1, 1931

The adrenals in 250 cases of congenital syphilis were studied. No instance of macroscopic gumma was noted. When spirochetes were found in congenital syphilis they were practically always demonstrable in the adrenal, without, however, being associated with any constant alteration in structure. Foci of blood-forming cells may be rather more striking than normally in the adrenal, owing apparently to prematurity, anemia, or both. Necrosis, with or without inflammatory changes, was present in the adrenal in some of the cases, but probably the most frequent and characteristic lesion of the adrenal is increase in the connective tissue of the capsule, frequently associated with active inflammatory changes.

HISTOLOGIC AND TOPOGRAPHIC STUDY OF CHRONIC GASTRITIS K. HILLENBRAND, Beitr. z. path. Anat. u. z. allg. Path. **85** 1, 1930

From Aschoff's institute comes this further contribution to the pathology of the gastric mucosa. Hillenbrand investigated the lesions of chronic gastritis with regard to their frequency, histologic character and topographic distribution. The stomach was removed as soon after death as possible and fixed in formaldehyde solution. Since previous investigations had established that chronic gastritis is most frequent after the middle period of life, the stomachs of persons over 35 years of age were examined. Twenty-one stomachs were found to be free of autolytic changes and suitable for study. Two each were from the fourth, fifth and ninth decades, four from the sixth decade, five from the seventh decade, and six from the eighth decade. Seven were from women and fourteen from men. The histologic alterations accepted as evidence of chronic gastritis were atrophy of the mucosa, increase in the number and size of lymphoid follicles and diffuse lymphocytic infiltration, the presence in the pylorus or in the fundus of mucosa of the type found in the small intestine or of pyloric glands in the fundus, and

hypertrophic thickening of the muscularis mucosae. For the description of the interesting technical procedure by means of which it was possible to examine histologically with a reasonable degree of completeness the entire gastric mucosa, the reader is referred to the original. Of the twenty-one stomachs that were examined, all but eight revealed the presence of the intestinal mucosa. Atrophic changes were present in four of the remaining eight stomachs. Chronic gastritis is more common in males than in females, since four of the seven stomachs of women failed to reveal chronic changes, whereas only four of seventeen stomachs of men were free from such changes. The transformation of gastric mucosa into intestinal mucosa may occur in localized areas or may be more diffuse or widespread. The localized transformation is held to be the result of metaplasia in the regenerative healing of acute inflammatory erosions of the mucosa, whereas the more diffuse process results from atrophy of the mucosa. Hillenbrand attempts to correlate the alterations noted with the pathologic physiology of gastric secretion. He concludes that chronic gastritis of the entire mucosa which leads to disappearance of glands from the fundus results in true achylia, which is not influenced by histamine. Chronic gastritis limited to the pylorus leads to an achylia that is overcome by histamine.

O T SCHULTZ

HYALINE GLOMERULI IN THE KIDNEYS OF NEW-BORN INFANTS AND NURSINGS

K. SCHULZ, Beitr z path Anat u z allg Path **85** 33, 1930

Herxheimer noted the presence of hyaline glomeruli in the kidneys of 80 per cent of new-born infants and nurslings examined by him and ascribed such glomeruli to maldevelopment and regression of incompletely developed glomeruli. Schwarz, in a later contribution on the subject, detected hyaline glomeruli in the kidneys of 80 per cent of nurslings over 3 weeks of age and in only 30 per cent of infants under this age. The greater frequency of hyalinization of the glomeruli after 3 weeks of age and the frequent association of the process with infiltrative and degenerative lesions of the kidney led Schwarz to conclude that hyaline glomeruli are the end-stage of an inflammatory process, brought about by postnatal infection or prenatal or postnatal toxic damage. Schulz, working in Herxheimer's laboratory, made a microscopic study of the kidneys of fifty-two fetuses and very young infants. His material consisted of eleven fetuses less than 48 cm long, fifteen new-born infants, eight nurslings up to 1 month of age, and eighteen nurslings over 1 month old. Hyaline glomeruli were seen in 90.3 per cent. The five cases in which such glomeruli were not found concerned fetuses less than 35 cm long. The most common localization of hyaline glomeruli was in the middle and deep zones of the cortex. They were as a rule present in otherwise normal kidneys, although occasionally associated with focal subacute inflammatory lesions in the kidneys of the older infants. Although focal inflammation may at times lead to hyalinization of isolated glomeruli, the occurrence of the process in the kidneys of fetuses and in kidneys that reveal no degenerative or inflammatory reactions leads Schulz to conclude that hyalinization of isolated glomeruli of infants is usually the result of maldevelopment.

O T SCHULTZ

Immunology

THE EFFECT OF DISEASES OTHER THAN DIPHTHERIA ON THE SCHICK TEST

BERNICE EDDY and A. GRAEME MITCHELL, Am J Dis Child **40** 985, 1930

Diseases such as measles and scarlet fever do not affect the reactions to the Schick test, that is, during the acute febrile and the convalescent stages of these diseases, there is no difference in the skin reaction to diphtheria toxin.

AUTHORS SUMMARY

THE EFFECT OF DISEASES OTHER THAN SCARLET FEVER ON THE DICK TEST
BERNICE EDDY and A GRAEME MITCHELL, *Am J Dis Child* **40** 988, 1930

Apparently, certain diseases during their acute febrile stages occasionally cause a positive Dick reaction to become negative. This does not occur regularly, and the evidence so far accumulated in the literature indicates that measles is especially apt to cause this depression in the skin reaction to scarlet fever toxin. There may be a delay in the skin reaction to injections of scarlet fever toxin so that erythema occurs at the site later than twenty-four hours after its injection. Whether this is a pseudoreaction or just what it signifies we are not prepared to state. In about 90 per cent of the patients, the skin reaction to a heat-killed suspension of scarlet fever streptococci was similar to that obtained with scarlet fever toxin. Great variation, which was probably not due to errors in the technic of injection, was encountered in the skin reaction to scarlet fever toxin in the acute and convalescent stages of scarlet fever. Some patients had positive reactions throughout the entire course of the disease and some had negative ones, others had reactions which varied from positive to negative or from negative to positive. About 30 per cent of the patients had positive reactions thirty-one days or longer after the onset of scarlet fever.

AUTHORS' SUMMARY

RAPIDITY OF IMMUNIZATION WITH DIPHTHERIA TOXOID M COOPERSTOCK and G F WEINFELD, *Am J Dis Child* **40** 1035, 1930

Observations are recorded on the rapidity of immunization with the routine employment of two injections of diphtheria toxoid, 1 cc each, with an interval of three weeks between injections. Of a group of fifty subjects retested three weeks after the second injection, twenty-nine, or 58 per cent, were found to give negative reactions to the Schick test. In a second group, consisting of forty-four subjects, it was found that thirty-five, or 79.5 per cent, gave negative reactions nine weeks after the second injection. In a third group of sixty-five subjects, sixty, or 92.3 per cent, showed a negative reaction from sixteen to twenty-two weeks after the second injection. Our results and those reported by others suggest that the employment of two injections of 1 cc each, three weeks apart, is, for practical purposes, an adequate routine procedure in diphtheria vaccination. It is pointed out that spacing the injections too closely may delay immunity.

AUTHORS' SUMMARY

THE TRYPANOCIDAL ACTION OF SPECIFIC ANTISERUMS ON *TRYPANOSOMA LEWISI* IN VIVO FRANCES A COVENTRY, *Am J Hyg* **12** 366, 1930

A passively transferable trypanocidal substance was demonstrated in serum obtained from rats during the course of uninfluenced infections with *Trypanosoma lewisi*. When the serum was tested in vivo against *T. lewisi* which had just appeared in the blood but had not yet undergone a number crisis, the trypanocidal power was manifested by a decrease in numbers or by the complete disappearance of the trypanosomes within from one to five hours after the injection of the serum. The presence of a trypanocidal substance in the serum during the course of infection is probably correlated with the occurrence of the first number crisis which occurs in uninfluenced infections with *T. lewisi* from about the sixth to the tenth day of infection. Serum obtained from rats shortly after the end of an uninfluenced infection exhibited a similar trypanocidal action when tested in the same way. Such serum was trypanocidal to trypanosomes tested either before or after the first number crisis. Serum tended to lose its curative power within a few weeks after the termination of infection. When serum obtained during or soon after the end of infection was given in graded doses to a series of rats, in certain series recurring zones of complete or partial action and of inaction tended to occur, i.e., the serum caused the complete disappearance or the diminution in number of

trypanosomes in certain doses of a series, was ineffective in slightly higher doses, was effective in still higher ones, and so on. The zonal phenomenon appeared to depend on the number of trypanosomes present in the rats at the time the doses of serum were administered. (a) when there were very few trypanosomes (from 1 to 20 per field), the serum tended to be effective in all doses, (b) when there were slightly more numerous trypanosomes (from 20 to 40 per field), the serum tended to show the zonal phenomenon, and (c) when there were very numerous trypanosomes (approximately 50 per field) the serum tended to be ineffective. The curative effect was more marked after the intravenous injection of the serum, but curative and zonal action followed either intravenous or intraperitoneal injection. Inactivation did not decrease the curative power of the serum. Moreover, the zonal phenomenon was independent of inactivation. Serum from rats and rabbits hyperimmunized against *T. lewisi* by repeated injections of the living parasites exhibited similar curative and zonal action.

AUTHORS SUMMARY

THE RELATION IN CHILDREN OF ERYTHEMA NODOSUM TO TUBERCULOSIS
LLOYD B. DICKEY, Am J M Sc 180 489, 1930

Erythema nodosum may occur in nontuberculous persons or in those infected with the tubercle bacillus. The great majority of cases of erythema nodosum in children are associated with a tuberculous infection, and most of the infections are initial and recent. Most children who have erythema nodosum exhibit marked hypersensitiveness to tuberculin given intracutaneously. In addition to the tuberculous infection, other conditions may be present which possibly influence hypersensitiveness to tuberculin. In many cases of erythema nodosum in children epituberculous lesions in the pulmonary parenchyma can be demonstrated by roentgenograms of the chest. In none of the patients observed in the series reported was a very active tuberculous lesion of the lung known to develop. The lesions of erythema nodosum, the epituberculous lesions and the positive skin reactions to tuberculin are similar histologically. As erythema nodosum in children is usually associated with early tuberculous infections, proper treatment for the latter condition gives a favorable prognosis as far as tuberculosis is concerned.

AUTHOR'S SUMMARY

TISSUE-IMMUNITY P. R. CANNON and G. A. PACHECO, Am J Path 6 749, 1930

This paper describes histopathologic studies of the skin and subcutaneous tissues of the abdominal wall of normal guinea-pigs and of those previously immunized by intracutaneous injections of a staphylococcus vaccine, which were infected by the intracutaneous injection of a live virulent culture of *Staphylococcus aureus*. The inflammatory responses were markedly different in the two groups. In the normal animals the inflammation was characterized mainly by an infiltration of polymorphonuclear leukocytes which actively phagocytosed the micro-organisms. In spite of this, the staphylococci showed no tendency to localize, but disseminated throughout the subcutaneous tissues in the form of a cellulitis. In the previously immunized animals, however, the staphylococci tended to remain localized near the site of inoculation where they were seen agglomerated in bacterial masses of various sizes, presenting the picture of a genuine agglutination in vivo. Coincidentally, the infiltration of cells of inflammation led to further localization of the micro-organisms so that only a localized area of necrosis resulted. The previous immunization by intracutaneous injections of the staphylococcus vaccine was followed by a marked thickening of the subreticular layer of the subcutis, due mainly to the activation or production of increased numbers of tissue macrophages. Evidence is presented that many of these are derived from agranulocytes of the blood. These macrophages were actively phagocytic for the live staphylococci and furnished an effective barrier against extension of the infection. The immunity secured by these procedures is predominantly cellular in type, with the tissue-

macrophages playing the dominant part, owing to increased numbers and also probably to increased metabolic activity. In addition, localization of the micro-organisms by the action of agglutinating or opsonizing antibodies is suggested as of primary importance in preventing the dissemination of the infectious agent. The combination of humoral and cellular mechanisms insures an adequate resistance against the bacterial invaders.

AUTHORS' SUMMARY

ANTIBODY FORMATION IN KALA-AZAR H. L. CHUNG and HOBART A. REIMANN,
Arch Int Med **46** 782, 1930

In patients with kala-azar and leukemia the immune response to typhoid vaccination shows a marked depression. After recovery from kala-azar, agglutinins are again formed normally.

AUTHORS' SUMMARY

SPECIFIC POLYSACCHARIDES FROM FUNGI H. D. KESTEN, D. H. COOK,
E. MOTT and J. W. JOBLING, J Exper Med **52** 813, 1930

From each of five yeastlike fungi and a *Trichophyton* a fraction which appears to be essentially a polysaccharide has been prepared. Tested by direct precipitation against the corresponding antisera, the polysaccharides from the yeastlike fungi exhibit only partial specificity. Cross-precipitation reactions are frequent. By absorption of precipitin on the intact mycotic bodies, however, a relatively high degree of specific precipitability can be demonstrated for the polysaccharides.

AUTHORS' SUMMARY

CHEMICAL AND IMMUNOLOGICAL PROPERTIES OF A SPECIES-SPECIFIC CARBOHYDRATE OF PNEUMOCOCCI W. S. TILLETT, W. F. GOEBEL and O. T. AVERY, J Exper Med **52** 895, 1930

Pneumococci contain a nonprotein constituent, which, on the basis of its chemical and immunologic properties, appears to be a carbohydrate distinct from the type-specific carbohydrate and common to the species.

AUTHORS' SUMMARY

TYPE-SPECIFIC PROTECTIVE ANTIBODY IN ANTIPNEUMOCOCCUS SERUM NOT NEUTRALIZED BY HOMOLOGOUS SPECIFIC SOLUBLE SUBSTANCE A. B. SABIN, J Exper Med **53** 93, 1931

The mutual relationship of the anticarbohydrate precipitins and of the protective action in antipneumococcus sera to the soluble specific substance was investigated. The assumption is made that there exists in antipneumococcus serum, a type-specific, protective antibody which is distinct from the anticarbohydrate precipitins and is not neutralized by the soluble specific substance. This assumption is based on the following observations in experiments which were conducted primarily with type 1 antipneumococcus horse serum. There was a lack of proportion between the quantity of specific soluble substance added and the amount of anticarbohydrate precipitin and protective action neutralized. The protective capacity of specific precipitates (specific soluble substance-precipitin complex) is accounted for on the basis of a liberation of nonspecifically adsorbed protective antibody. Specific soluble substance only partially neutralizes the protective action of antipneumococcus serum *in vivo*. The type-specific protective antibody remains in antipneumococcus serum after complete precipitation of the anticarbohydrate precipitins. This residual type-specific protective antibody is not neutralized by additional specific soluble substance nor by absorption with heterologous pneumococci, it is definitely absorbed by the homologous pneumococci.

AUTHOR'S SUMMARY

THE EFFECT OF ALEXIN ON MIXTURES OF ROUS SARCOMA VIRUS AND ANTI-VIRUS J HOWARD MUELLER, J Immunol **20** 17, 1931

Antibodies against the agent of the Rous fowl sarcoma were produced in geese, ducks and rabbits by injections of suspensions of the sarcoma, and in chickens by injections of similar suspensions which had been heated. The viricidal effect is enhanced by an hour's incubation at 37 C with fresh, unheated guinea-pig complement, heating at 50 C for fifteen minutes destroys this effect.

AUTHOR'S SUMMARY

THE ACTION OF FORMALDEHYDE ON DIPHTHERIA TOXIN W E BUNNEY, J Immunol **20** 47, 1931

Evidence is offered which indicates that the formation of toxoid is not the result of the direct action of free formaldehyde on the diphtheria toxin. Results are obtained which suggest that the formation of toxoid by the action of formaldehyde on diphtheria toxin may depend on a compound resulting from the reaction between formaldehyde and the amino group in an amino-acid. A possible method for making acceptable toxoid from lower grade diphtheria toxins is suggested.

AUTHOR'S SUMMARY

SEROLOGIC STUDIES ON THE PROTEINS FOUND IN CASEIN D C CARPENTER and G J HUCKER, J Infect Dis **47** 435, 1930

It has been shown that the proteins occurring in crude casein and having molecular weights, respectively, of 98,000, 188,000 and 375,000 are clearly distinguishable from one another by serologic reactions. The production of co-precipitin specific for a heated antigen and the distinguishing of it from unheated antigen has been recorded. The alcohol-soluble protein of Osborne and Wakeman does not appear to be the same as the acid-alcohol soluble protein having a molecular weight of 375,000.

AUTHORS' SUMMARY

ERROR IN GROUPING FROM CONTAMINATION WITH 'MUSTARD BACILLUS'—TRANSFUSION OF INCOMPATIBLE BLOOD E F GROVE and M J CRUM, J Lab & Clin Med **16** 259, 1930

Owing to contamination of a serum with a "mustard bacillus," which produces a nonspecific power to clump human corpuscles of all groups, a patient of group O was given a transfusion of 300 cc of group B blood. Fortunately, no harmful reaction developed, probably because the agglutinin did not clump B corpuscles at the temperature of the body.

THE TITRATION OF SCARLATINAL ANTITOXIN BY SKIN TEST IN CHINCHILLA RABBITS F H FRASER and H PLUMMER, Brit J Exper Path **11** 291, 1930

A series of dilutions was made of each antitoxin to be tested, and 2 cc of each dilution was mixed with an equal amount of toxin dilution, incubated at 37 C for one hour and injected into rabbits and human beings intradermally. A comparison of the results in the rabbits and human beings showed little difference. The accuracy of the skin titration was found to be within similar limits for rabbits and human beings, provided half as many more animals were used in the test. Two antitoxins could be differentiated by skin titration, if the potency of one was twice that of the other. Small differences in potency were not demonstrable by the method described.

EDNA DELVES

SWARTZMAN'S PHENOMENON OF LOCAL SKIN REACTIVITY TO BACTERIAL PRODUCTS F M BURNET, J Path & Bact **34** 45, 1931

The Shwartzman reagent is common to widely different bacterial groups. If material from *B. typhosus*, *meningococcus* or *B. pertussis* is used to prepare the skin, preparations from any of these organisms will give typical reactions when injected intravenously. Active preparations are readily obtained by Besredka's method of preparing "endotoxins," and the evidence points to the Shwartzman reagent being identical with these bodies. Local and general desensitization of prepared areas can be obtained by suitable injections. Material treated with formaldehyde can function as a provocative agent when it is injected intravenously, but when it is used to prepare the skin it gives an atypical reaction characterized by a central desensitization of varying extent, often sufficient to annul the reaction completely. The points of resemblance and of dissimilarity to anaphylactic reactions shown by the Shwartzman phenomenon are discussed.

AUTHOR'S SUMMARY

THE INTERMEDIATE ZONE PHENOMENON IN CERTAIN BR. ABORTUS AGGLUTINATING SERA F W PRIESTLEY, J Path & Bact **34** 81, 1931

A curious zone of inhibition seen in certain serums from cattle affected with contagious abortion has been investigated. The following points have been demonstrated. The position of the zone depends on the ratio between the amount of serum and the organisms. Filtration through bacteriologic filters causes the zone to widen in the direction of stronger concentrations of serum. Heat (56 C.) in the absence of the organisms widens the zone, but in the presence of organisms causes the zone to narrow. The marked effect of saline in varying concentrations on the zone has been demonstrated. Experiments suggest that the zone is due to an insufficient reduction of potential on the bacteria in the dilutions within the zone.

AUTHOR'S SUMMARY

AUTOPSIES ON FIFTY CHILDREN VACCINATED WITH BCG J ZEYLAND and E PIASECKA-ZEYLAND, Ann de l'Inst Pasteur **43** 767, 1929

Children who had died from causes other than tuberculosis were carefully examined. They had received oral administrations of BCG vaccine. Lesions were not produced even in premature or weakened infants. The organisms may traverse the digestive tract, but prolonged sojourn in the body does not increase their virulence, although sensitivity to tuberculin develops. For four weeks following vaccination, or until immunity is established, it is necessary to prevent the tuberculous infection of the vaccinated infant.

M S MARSHALL

VACCINATION OF MAN AGAINST UNDULANT FEVER C DUBOIS and N SOLLIER, Ann de l'Inst Pasteur **45** 596, 1930

Preventive vaccination has been accomplished on 111 persons who had been exposed to *Brucella* infection (caprine, ovine, or bovine). No subjects vaccinated from three to eight months previously have actually contracted undulant fever. Two of thirty-six nonvaccinated controls were attacked. It is thus concluded that in regions in which animal brucellosis exists, preventive vaccination is the only practical means of protecting man. In "contaminated" regions vaccination should be practiced on those coming in contact with infected animals. The vaccine that we used is entirely innocuous. (The vaccine consists of heat-killed suspensions of human, ovine, caprine, porcine and bovine cultures at a total of two billion organisms per cubic centimeter.) The duration of immunity can be determined only by longer experience with more vaccinations, the practical value of the method rests on this determination.

AUTHORS' SUMMARY

THE LYSOZYME CONTENT IN THE CONJUNCTIVAL SAC AND IN THE TEARS C
HALLAUER, Arch f Augenh 103 199, 1930

The lysozyme content of the tears was determined in 120 patients who had (a) clinically normal conjunctivae, and (b) chronic and acute inflammations of the conjunctiva or cornea. The lysozyme content was always decreased in acute irritations of the anterior eye accompanied by abundant secretion of tears, or as the result of general disease (scrofulosis, lymphatic diathesis). It would appear, therefore, that the amount of lysozyme found in the tears is immediately dependent on the secretory activity of the lacrimal glands, it is decreased primarily by general diseases and secondarily by a hypersecretion induced by reflex. Atropine prevents the hypersecretion of tears and therefore tends to increase the amount of lysozyme, whereas in stimulating secretion, pilocarpine lowers the lysozyme content.

The significance of lysozyme as an antibacterial substance is demonstrated and its therapeutic use recommended

AUTHOR'S SUMMARY

DIPHTHERIA PROPHYLAXIS BY MEANS OF LOEWENSTEIN'S DIPHTHERIA CULTURES IN VACCINE OINTMENT E. URBANITZKY, Deutsche med Wchnschr 56 1342, 1930

To prevent diphtheria in a children's hospital the infants and children were inoculated three times at intervals of two months by rubbing increasingly large doses of unfiltered diphtheria cultures treated with formaldehyde into the skin. Of twenty-four children up to the age of 2 years, fifteen gave positive reactions to the Schick test. Six months after the treatment was started all gave negative reactions to the Schick test. This method of immunization was slightly less successful in older children, and of twenty-three adults who had been treated, only 63 per cent gave negative reactions to the Schick test. The incidence of diphtheria among the children in the hospital was reduced to nil.

PAUL BRESLICH

CEREBRAL IMMUNIZATION AGAINST DIPHTHERIA TOXIN U. FRIEDSMANN and A. ELKELES, Klin Wchnschr 9 1907, 1930

In rabbits the immune response obtained through the intracerebral injections of diphtheria toxin is much greater than that obtained through intravenous injection.

EDWIN F. HIRSCH

IMMUNITY REACTIONS IN SYPHILIS H. KROO and N. V. JANCsó, Klin Wchnschr 10 105, 1931

A serum resistant variant of *Spirochaeta pallida* may be produced by gradual adjustment to immune serum. These resistant spirochetes lose their ability to stimulate spirocheticidal antibodies, but retain the property of provoking complement-binding substances. Inoculation of the serum resistant spirochetes into ordinary mediums leads to a recovery of the antigenic properties.

AUTHORS' SUMMARY

THE MECHANISM OF DESENSITIZATION OF THE ALLERGIC SKIN W. STORM VAN LEEUWEN, Ztschr f Immunitätsforsch u exper Therap 69 1, 1930

In the case of sensitization to various substances, desensitization by means of a particular antigen usually results in a local desensitization to other antigens as well. The question whether this desensitization is dependent on an "intermediary substance" is discussed.

BACTERIAL LIPOIDS M. GUNDEL and W. WAGNER, Ztschr f Immunitätsforsch u exper Therap 69 63, 1930

Various bacterial lipoids are bactericidal due to their content of fatty acids. The antigenic and bactericidal properties of bacterial lipoids are not identical.

THE ANTIGENIC GROUPING OF THE COLON BACILLI M GUNDEL, Ztschr f Immunitätsforsch u exper Therap **69** 99, 1930

The colon bacilli fall into various antigenic groups, all of which have certain common antigenic properties

CHEMICAL NATURE OF HETEROGENETIC ANTIGEN IN SHIGA BACILLI K MEYER, Ztschr f Immunitätsforsch u exper Therap **69** 134, 1930

The heterogenetic antigen in Shiga bacilli is not attached by pepsin or trypsin and resists treatment with sodium hydroxide at 100 C for one hour, but hydrochloric acid destroys it promptly. Consequently, it seems highly improbable that the antigen is of protein nature, and the claim that it is a carbohydrate seems to be strengthened

AN UNUSUALLY HIGHLY DEVELOPED ANAPHYLACTIC STATE IN THE GUINEA-PIG R DOERR and S SEIDENBERG, Ztschr f Immunitätsforsch u exper Therap **69** 169, 1930

After passive sensitization to horse serum by means of specific rabbit serum, guinea-pigs may die from shock after the intravenous injection of 0.002 cc of horse serum. Congenitally sensitized pigs may suffer fatal shock from 0.0008 cc of horse serum injected intravenously, and such pigs may die from shock even when the horse serum (from 0.2 to 2 cc) is introduced subcutaneously, in the latter case, however, the symptoms develop only after a latent period of from fifteen to twenty-five minutes

Microbiology and Parasitology

DIPHTHERIA OF THE UMBILICUS J C MONTGOMERY, Am J Dis Child **40** 968, 1930

The case of an infant with umbilical diphtheria complicated by postdiphtheritic paralysis and myocarditis is reported, with complete bacteriologic and pathologic observations and a brief review of the literature. It has been impossible to discover in the literature another case of diphtheria limited solely to the umbilicus in which there were myocardial or neurologic complications

AUTHOR'S SUMMARY

SONNE DYSENTERY RICHARD L NELSON, Am J Dis Child **41** 15, 1931

Attention is drawn to the possible importance of *B dysenteriae* Sonne as a cause of dysentery in children. Methods for the isolation and identification of the Sonne bacillus are given. Clinical features of the disease with case histories and clinical charts illustrative of the mild and severe forms are given

AUTHOR'S SUMMARY

ULCERATIVE LARYNGITIS DUE TO CORYNEBACTERIUM ULCERANS JESSE G M BULLOWA and MENDEL JACOBI, Am J Dis Child **41** 120, 1931

A case of fatal ulcerative laryngitis due to an atypical diphtheria-like organism and producing only a slight fibrinous reaction is reported. The organism cultured from a laryngeal ulcer is identified as the *Corynebacterium ulcerans* of Gilbert and Stewart, previously isolated only from nonfatal upper respiratory infections. Both organisms produce extensive necrosis and ulceration without the formation of typical diphtheritic pseudomembrane. The immunologic study of cases of diphtheria not responding to antitoxin is suggested

AUTHORS' SUMMARY

DEATH IN INFECTIONS WITH *TRYPANOSOMA EQUIPERDUM* IN RATS JUSTIN ANDREWS, CARL M JOHNSON and V J DORAMI, Am J Hyg **12** 381, 1930

It is believed that *T equiperdum* causes death, by asphyxiation, of the rat host into which it is experimentally introduced. This is brought about by pulmonary edema due to partial obstruction of the circulation by the agglutination of the trypanosomes in the heart and lungs. The consequent anoxemia leads to a nonvolatile, uncompensated acidosis and to central necrosis of the liver, interfering with both its glycogenic and its glycogenolytic functions and ultimately producing hypoglycemia.

AUTHORS' SUMMARY

EXPERIMENTAL AMEBIASIS IN KITTENS Kentaro Hiyeda, Am J Hyg **12** 401, 1930

It is attempted to explain the manner of invasion into the tissues of the colon by *Entameba histolytica*, experimentally injected rectally into a limited number of kittens. In the cases showing *E histolytica* in the stools during the first twelve hours after injection, the mucosa of the colon displays minute follicular ulcerations, and the superficial capillaries are engorged with leukocytes. Up to forty-eight hours following injection, the colitis produced is typical of any acute colitis, and no ameba can be demonstrated in the tissue. Thereafter, different sized, ulcerated areas appear in the mucous membrane of the colon, and microscopically their walls appear coated with tissue debris, mucus, plasma and amebae. A new conception of the mode of invasion is presented. From the superficial ulcers in the mucous membrane, the ameba spread laterally along the collagenous fibers of the submucosa and also through the membrana propria. The deep submucosa is invaded and Lieberkuhn's glands are in turn invaded from their basal side. Following this the epithelium exfoliates at the basal membrane, and the amebae occupy the empty spaces. The submucosa is invaded by way of the fibrous tissue, and not through the lumina of Lieberkuhn's glands.

P H GUINAND

RHINOSPORIDIUM SEEBERI PATHOLOGICAL HISTOLOGY AND REPORT OF THE THIRD CASE FROM THE UNITED STATES C V WELLER and A D RIKER, Am J Path **6** 721, 1930

The first description of *Rhinosporidium seeberi* was published in a thesis from Buenos Aires in 1900 by Guillerino Seeber, and since that time there have appeared in the literature at least twenty-five case reports from India and Ceylon, several of them dealing with the occurrence of infection in anatomic locations other than the nose. Three cases of this parasitic infection have been reported from Argentina and three widely scattered cases from the United States. In no instance is there any certainty concerning the mode of infection and transmission. The possibility of an animal host, probably among the larger farm animals, seems logical in view of a history, in most cases, of exposure to such animals. All efforts at experimental animal inoculation, however, have given negative results. It seems remarkable that not one of the thirty or more cases reported has been in the female. The gross lesion in the nose is described as a reddish-purple, raspberry-like polypus, which externally presents no features attracting particular attention. A close examination of the cut surface, however, reveals the larger parasites as white spots of pinpoint size. Histologically, a moderately edematous, vascular, connective tissue stroma is observed peppered with characteristic parasitic cysts, each a single organism in various stages of development. The cysts average 100 microns in diameter, being surrounded by a doubly contoured chitinous-appearing capsule. The mature cysts contain many spores, which on rupturing are followed by a local proliferative foreign-body reaction in the polypus.

C G WARNER

NEUROVACCINIAL AND HERPETIC MENINGO-ENCEPHALITIS IN RABBITS E T C
SPOONER, Am J Path **6** 767, 1930

The histologic observations in six neurovaccinal and four herpetic brains are described. Intranuclear inclusion bodies are found to be the only sure distinctive feature of the herpetic disease. In other respects the two diseases are essentially similar. In neurovaccinia, the meningitis is the most conspicuous observation, both clinically and histologically. Various spontaneous lesions in the brains of uninoculated laboratory rabbits are discussed. Changes in the myelin sheaths are described in the brains of herpetic and vaccinal animals, but perivascular demyelination of the kind characteristic of postvaccinal encephalitis in man was not seen. It is possible that the duration of the disease is a factor in the development of such a condition. Since preparing this paper for publication, valuable articles on the histology of neurovaccinal encephalitis in monkeys and rabbits, by Hurst and Fairbrother and by McIntosh and Scarff, have appeared in the *Journal of Pathology and Bacteriology* (**33** 463 and 483, 1930). These papers are in agreement on the cardinal points of histology, such as the absence of inclusion bodies and the accentuation of the meningitis. In neurovaccinia, McIntosh and Scarff emphasize the rôle of the vascular endothelium, this is undoubtedly damaged in the smaller vessels, and there are occasional evidences of its proliferation, but from the preparations in this investigation the impression is derived that this feature of the disease is subsidiary to the general inflammation, and, moreover, it seems to be just as much a feature of herpetic encephalitis as it is of neurovaccinal encephalitis.

AUTHOR'S SUMMARY

THE IDENTITY OF YELLOW FEVER LESIONS IN AFRICA AND AMERICA OSKAR
KLOTZ and T H BELT, Am J Trop Med **10** 299, 1930

In our studies we have found that the quality of the lesions arising in yellow fever in Africa is similar to that of lesions occurring in American cases. Furthermore, the incidence of various types of changes in different tissues is broadly the same, with differences only in a few reactions which may be accounted for by the technic applied. In these more careful studies, applied to a larger number of cases, we have confirmed our previous observations that the nature of the pathologic processes arising in the yellow fever of Africa is identical with that of such processes occurring in American cases. Variations that have been observed in the quality of the lesions here described are compatible with the variations that have been found in different strains of virus isolated in America and in Africa.

AUTHORS' SUMMARY

CALABAR SWELLING IN LOA PATIENT ASA C CHANDLER, GIBBS MILLIKEN and
VICTOR T SCHUHARDT, Am J Trop Med **10** 345, 1930

The appearance of three Calabar swellings on distant parts of the body of a patient infected with *Loa* worms following the release of some of the body fluids of a *Loa* worm under the conjunctiva at the time of its extraction, together with the production of a typical Calabar swelling by the injection of a filarial antigen, affords strong, if not conclusive, evidence for the allergic nature of these swellings, as first suggested by Fulleborn.

AUTHORS' SUMMARY

THE TROPICAL RAT MITE AS THE CAUSE OF A SKIN ERUPTION AND VECTOR OF
ENDEMIC TYPHUS FEVER BEDFORD SHELWIRE and WALTER E DOVE, J A M A
96 579, 1931

Approximately 200 cases of "rat mite dermatitis" are reported from Dallas, Texas, and neighboring towns. From persons having evidence of mite bites, and from their residences or places of work, mites were collected and identified as *Liponyssus bacoti* Hirst. At Dallas, Fort Worth, Henderson and Longview, Texas,

mites were collected from rats and were identified as *Liponyssus bacoti*. In the same places, 11 proved cases and approximately 125 cases of suspected endemic typhus were reported. The advent and coincidental occurrence of endemic typhus and the tropical rat mite in northern and eastern Texas suggest that these parasites may be vectors of the disease.

AUTHORS' SUMMARY

THE TRANSMISSION OF PERIODIC OPHTHALMIA OF HORSES BY A FILTRABLE AGENT
ALAN C. WOODS and ALAN M. CHESNEY, J. Exper. Med. **52** 637, 1930

A filtrable agent has been obtained from the humors and tissues of the eyes of horses suffering from active periodic ophthalmia. The intravitreal injection of this filtrate produced in normal horses the same clinical and pathologic picture observed in the natural disease. When injected into rabbits, the filtrate produced a different clinical picture, but the essential pathologic lesions closely resembled those found in horses. After passage of the filtrable agent through six generations of rabbits, it again produced the clinical and pathologic picture of the natural disease when injected into the eyes of normal horses. It appears, in this epidemic at least, that this filtrable agent was the specific etiologic factor of the periodic ophthalmia.

AUTHORS' SUMMARY

TYPHUS FEVER. H. ZINSSER and M. RUIZ CASTANEDA, J. Exper. Med. **52** 865, 1930

In guinea-pigs inoculated with washed *Rickettsiae* from Mexican typhus fever a disease develops identical with that resulting from inoculations with whole tunica sciapings, blood or other virulent material, and the animals thereby become immune to European typhus fever. The etiologic agent of Mexican typhus fever is the *Rickettsia* body of the type described by Mooser in the tunica vaginalis of infected guinea-pigs. It is likely that the etiologic agent of European typhus fever is an organism similar to this, but not identical with it in some of its minor biologic characteristics.

AUTHORS' SUMMARY

THE INTRA-AURAL ADMINISTRATION OF CERTAIN BACTERIA ASSOCIATED WITH MIDDLE EAR DISEASE IN ALBINO RATS. J. B. NELSON, J. Exper. Med. **52** 873, 1930

The infective capacity of three bacteria commonly encountered during a study of natural disease of the middle ear in a rat colony has been determined by direct intra-aural injection into young rats. One week after the introduction of *B. actinoides*, 75 per cent of the rats showed a purulent exudate in the middle ear cavity into which the injection was made, and 65 per cent yielded pure cultures of the organism. With hemolytic and nonhemolytic streptococci, 75 per cent showed a serous or mucoid exudate, and 12 per cent yielded the organism in culture. With a diphtheroid, 18 per cent showed a gross reaction in the middle ear which was sterile in every case. The experimental observations are discussed in relation to the etiology of disease of the middle ear.

AUTHOR'S SUMMARY

STREPTOCOCCI IN INFECTIOUS ARTHRITIS AND RHEUMATIC FEVER. R. N. NIEL and E. A. WAXELBAUM, J. Exper. Med. **52** 885, 1930

On using the technic described by Cecil and his associates in chronic infectious arthritis, only one positive culture, a diphtheroid, was obtained in ten cases of chronic infectious arthritis and sterile cultures in eleven cases of infectious arthritis and twelve cases of rheumatic fever. A second series was studied, the technic described by Cecil in rheumatic fever being used. Synovial fluid, lymph glands and subcutaneous nodules, as well as the blood were cultivated. Seven different organisms were isolated. Since the same organism was not found in duplicate cultures, the authors believe their positive results to be due to contaminations.

L. E. COOLEY

STUDIES ON TUBERCULOSIS I REACTION OF THE CONNECTIVE TISSUES OF THE NORMAL RABBIT TO LIPOIDS FROM THE TUBERCLE BACILLUS, STRAIN H-37, II REACTION OF THE CONNECTIVE TISSUES OF THE NORMAL RABBIT TO A WATER-SOLUBLE PROTEIN AND A POLYSACCHARIDE FROM THE TUBERCLE BACILLUS, STRAIN H-37 SPONTANEOUS PSEUDO-TUBERCULOSIS ASPERGILLINA AS A COMPLICATION IN FRACTION TESTING, III THE DERIVATION OF GIANT CELLS WITH ESPECIAL REFERENCE TO THOSE OF TUBERCULOSIS, IV THE RELATION OF THE TUBERCLE AND THE MONOCYTE-LYMPHOCYTE RATIO TO RESISTANCE AND SUSCEPTIBILITY IN TUBERCULOSIS F R SABIN, C A DOAN and C E FORKNER, *J Exper Med* (supp no 3), 1930, p 1

I The lipid fraction from the tubercle bacillus contains maturation factors for monocytes, epithelioid cells and epithelioid giant cells. The most important component of the lipoids for biologic investigation is the phosphatide A-3, since it produces the most massive reaction toward epithelioid cells and epithelioid giant cells, and also because it is the only partition of the lipoids that acts as an antigen. The stimulus to the formation of tubercles resides in certain fatty acids of high molecular weight found in tubercle bacilli. These fatty acids are present in the four major partitions of the lipoids and account in each instance for their specific activity. The most potent fatty acid in the production of tubercles is that derived from the phosphatide. The purified, optically active phthioic acid obtained from the glyceride fraction, in small dosage, produces epithelioid cells, but more non-specific connective tissue, the optically inactive tuberculostearic acid is relatively inert. The specific tuberculous tissue resulting from the intraperitoneal injection of the phosphatide from the tubercle bacillus undergoes resorption. Two mechanisms in its disappearance similar to those operating in the disease have been seen: caseation in which masses of degenerating epithelioid cells become infiltrated with leukocytes, and phagocytosis of the cellular debris by clasmotocytes, without caseation. Besides the specific reaction of the lipoids, these factors also produce a marked growth of nonspecific connective tissue cells, without, however, any reaction toward fibrous tissue in the acute stages. All the subfractions from the lipoids are irritating when injected into the peritoneal cavity, calling leukocytes into the tissues and stimulating clasmatocytic activity. The unsaponifiable substance from the purified wax is particularly active in producing an extreme general reaction of connective tissue cells.

II From these studies we conclude that the water-soluble protein from the tubercle bacillus, when not denatured, is toxic to normal rabbits, inducing fever and hemorrhage when introduced intravenously, but it is not lethal except in massive doses. By the intraperitoneal route it is less toxic, but calls forth a local response of leukocytes and phagocytes without any striking proliferation of new connective tissue. Damage to the endothelium is indicated by hemorrhage, chiefly in the bone marrow. Tuberculous guinea-pigs succumb rapidly to protein 304 when given intraperitoneally. The polysaccharide is nontoxic when introduced intravenously into the normal animal, when introduced intraperitoneally, on the other hand, it is irritative, and each succeeding dose continues to elicit a fresh emigration of leukocytes from the vessels. These leukocytes appear to be damaged, for they are actively engulfed by clasmotocytes. Guinea-pigs with extensive tuberculosis may die soon after subcutaneous or intraperitoneal injections of the polysaccharide. *Aspergillina* fungus may produce a pseudotuberculous lesion, resembling, both macroscopically and microscopically, the cellular reaction of tuberculosis. The absence of positive skin tests with old tuberculin when such lesions are present, as furthermore when tuberculous tissue has been produced by chemical stimulation with the tuberculophosphatide, emphasizes the necessity for considering tubercle formation as a mechanism apart from allergy in tuberculosis.

III There are two types of giant cells discriminated by their method of formation, one is derived from a single monocyte or epithelioid cell and the other by the fusion of cells. The epithelioid giant cell is formed by amitotic nuclear division, it tends to be small, simple and relatively uniform in structure, its

essential structure is a rosette of fine vacuoles which in the living state are stainable with neutral red. The foreign body types show extreme variation in size and structure, according to the nature and the number of the cells out of which they are made. They lack any constant cytoplasmic pattern. Both of these types of giant cells are probably formed in response to the need for phagocytosis of foreign material. In tuberculosis it is probably only certain specific portions of the lipoids that induce the production of mononucleated and multinucleated epithelioid cells. The stimuli for the formation of giant cells of the foreign body type are much more varied than those that produce epithelioid giant cells.

IV In rabbits receiving a standard dose of bovine tubercle bacilli, a high preinfection monocyte-lymphocyte ratio in the circulating blood has been correlated with the development of an acute fulminating tuberculous infection, but with an average or low index, the course of the disease has varied. Susceptibility has been further marked by the promptness with which the monocyte-lymphocyte index rose after infection and with its maintenance at a high level, resistance, on the other hand, has been evidenced by a continued low index. The monocyte-lymphocyte index is one measure of resistance to tuberculosis. Some evidence has been presented to show that when monocytes, the forerunners of the epithelioid cell, are decreased through the action of an antiserum, a greater proportion of the animals survive into the chronic stage of the disease than do the controls. The production of tuberculous tissue in considerable quantity by injection into the tissues of the phosphatide or liquid saturated fatty acid from the tubercle bacillus does not render the animal allergic, and seems definitely to lower resistance to the disease on subsequent infection with tuberculosis. The degree to which the tissues react specifically with the formation of new epithelioid cells is indicated by the amount of the change in the monocyte-lymphocyte index in the blood. The differences observed in individual animals in the amount of tissue reaction to a given amount of phosphatide derived from the tubercle bacillus are definite and are similar to those long noted in connection with humoral antigen-antibody responses with proteins. Both in tuberculosis and after intraperitoneal injections of the phosphatide, the relationship of monocyte to lymphocyte in the blood before death has been a measure of the extent of the epithelioid and lymphoid proliferation found at autopsy. Hence, the monocyte-lymphocyte ratio can be taken as an index of the relative abundance of these cells in the tissues. Antigenic intravenous doses of the phosphatide, or of antiphosphatide serum, given either before or after infection, may give a slight protection to an animal if the dose of infecting organisms is not too great. Taken together, the observations of the present paper implicate the monocyte and its derivative, the epithelioid cell, when harboring living bacilli, as factors in the spread of tuberculosis in the animal. The type of reaction of an animal to the lipoids of the tubercle bacillus, whether predominately cellular or humoral, may be a decisive factor in determining resistance on the one hand and susceptibility on the other.

AUTHORS' SUMMARIES

BORIC ACID FOR THE PRESERVATION OF MILK NATURALLY INFECTED WITH *BRUCELLA ABORTUS* J. TRAUM and B. S. HENRY, J. Infect. Dis. **47** 380, 1930

Boric acid in 1 per cent concentration is a convenient, efficient and safe preservative for milk that is to be injected into guinea-pigs to determine the presence or absence of *Brucella abortus*.

AUTHORS' SUMMARY

THE GROWTH AND TOXIN PRODUCTION OF *CORYNEBACTERIUM DIPHTHERIAE* IN SYNTHETIC MEDIA M. E. MAVLR, J. Infect. Dis. **47** 384, 1930

The synthetic medium devised by Braun and Hofmeier was found to afford a better basic medium for the study of growth and toxin production of *C. diphtheriae* than the medium of Uschinsky, Hadley or Dolloff. The comparative nutritive values of ten amino-acids were studied, three strains of Park 8 and three more

recently isolated strains being employed. The simple mono-amino-acids, such as alanine, phenylalanine, valin and especially glycine, were more effective in stimulating growth in a synthetic medium than the more complex mono-amino-acids that were tried. The nitrogen-bearing constituents of the Braun and Hofmeier medium were modified considerably before moderate production of toxin was obtained. The cystine content was increased fourfold, to the point of maximum solubility in this solution, asparagin or ammonium succinate replaced the sodium aspartate, and glycine was added. A virulent strain, 4703, one strain of Park 8 and an avirulent strain, 4104, were adapted to growth on synthetic mediums. The virulent strain 4703S produced toxin on synthetic mediums after six months' cultivation on protein-free mediums. The most potent toxin produced by strain 4703S had a minimal lethal dose of 0.1 cc and a skin test dose of 0.0001 cc. Strain Park 8T elaborated a weaker toxin in synthetic mediums, with a minimal lethal dose of 0.5 cc and a skin test dose of 0.0005 cc. The experiments described seem to indicate that several factors control the production of toxin in synthetic mediums. It appears that the strain must be thoroughly adapted to rapid growth and formation of pellicle in protein-free medium. It appears, further, that the medium must provide not only nutrients for growth and pellicle formation, but these nutrients should also favor the appearance or maintenance of the toxigenic variants that occur in consequence of a dissociative process.

AUTHOR'S SUMMARY

EXPERIMENTAL RABIES IN WHITE MICE AND ATTEMPTED CHEMOTHERAPY
A HOYT and C W JUNGBLUT, J Infect Dis 47 418, 1930

Typical and constant rabies may be produced in white mice by intracerebral injection of fixed virus. A dose of virus approximating a minimum lethal dose may be determined. Prophylactic administration of various drugs (particularly arsenicals and quinine derivatives) failed to protect animals infected intracerebrally by single or multiple minimal lethal doses. The period of incubation of the disease consistently showed a very slight prolongation following injection of silver arspheganine.

AUTHORS' SUMMARY

THE IDENTIFICATION OF A STREPTOTHRIX ISOLATED FROM A HUMAN BEING
INFECTED WITH IT G MEHRTEN and R S MUCKENFUSS, J Infect Dis 47 425, 1930

Reports of infections with *Streptothrix* have been accumulating for many years. Although clinical data are fairly abundant, bacteriologic data are incomplete in most of the reports of cases. The accompanying table gives the characteristics in some cases reported in the literature, as well as the characteristics of the strain isolated at Barnes Hospital. Bacteriologic studies in many reports were not extensive enough to make their inclusion in this table practical. Those cases in which the organisms formed granules in tissue or pronounced swellings at the ends of the filaments in culture were not included. Only a few studies on the fermentation of sugars by this organism are reported in the literature. The organism isolated by Giddings did not ferment dextrose, lactose, saccharose or mannite. Neither did it produce hemolysis. The strain isolated by Blake from a case of rat-bite fever did not ferment dextrose, inulin, lactose, mannite, raffinose, saccharose or salicin. Serologic studies were made by Claypole, who used the complement-fixation reaction. The serums showed cross-reactions with other members of the group, as well as with tubercle and lepra bacilli, so that the method was not satisfactory for classification. It is evident from a review of the literature that the strains of *Streptothrix* that have been described differ markedly in their characteristics as observed by ordinary bacteriologic methods. Any further subdivision of the group by the present methods of study is impracticable and of no significance as regards the type of disease. The strain that we have isolated approaches most nearly in its characteristics that described by Horst

AUTHORS' SUMMARY

TYPES OF BRUCELIA IN ONE HUNDRED AND TWENTY-NINE CASES OF
UNDULANT FEVER W N PLASTRIDGE and J G McALPINE, J Infect
Dis 47 478, 1930

One hundred and twenty-nine strains of the genus *Brucella* isolated from cases of undulant fever in the United States and Europe were classified by Huddleson's dye plate method and by their ability to utilize dextrose. Sixty-three of these strains were found to be of the bovine type of *B. abortus* and the remaining sixty-six of the porcine type. The average, minimum and maximum amounts of available (1 per cent) dextrose utilized by the two types of *B. abortus* of human origin are as follows: bovine type, 0.88 per cent, none and 3, respectively; porcine type, 10 per cent, 3.3 per cent and 18.2 per cent, respectively. The results obtained by Huddleson's dye plate method were in close agreement with those obtained by the dextrose utilization method.

AUTHORS' SUMMARY

DECOMPOSITION OF UREA BY BACILLUS PROTEUS A A DAY, W M GIBBS,
A W WALKER and R E JUNG, J Infect Dis 47 490, 1930

Bacillus proteus was cultivated in plain, dextrose urea and urea-dextrose urea broths. Dextrose exerted a sparing action for the protein, but in the urea broth increased the formation of ammonia. When, however, the markedly greater number of organisms in the dextrose urea broth, attributable to the maintenance of a more favorable reaction for growth by the interaction of the end-products of dextrose and the breakdown of urea, is considered, it becomes apparent that less hydrolysis of urea per unit volume of organisms occurred than in the plain urea broth. The same mechanism was responsible for the greater destruction of dextrose observed in the presence of urea. In actively growing cultures of *B. proteus* in urea broth, a very small amount of growth brought about a marked breakdown of urea, whereas massive growths of organisms that were not reproducing (resting) were required to produce an equivalent change. With the latter, the urea-splitting was roughly proportional to the mass of the organisms. Urea did not meet the nitrogen requirements of the organism, as tested in a variety of synthetic mediums. The inference is warranted that the urea activity is only incidental to the metabolism of the organism and not concerned with its vital needs. Great difference in morphology was encountered when *B. proteus* was cultured on plain agar, dextrose agar and urea agar. Further confirmation of the endocellular nature of the enzyme was found in the ability of chloroform-killed, washed organisms to hydrolyze urea. Organisms so killed were decidedly less effective than vigorously reproducing bacteria. The addition of dextrose to the urea solution augmented the urease activity of moist chloroform-killed organisms, but was without influence on dried chloroform-killed organisms.

AUTHORS' SUMMARY

HUMAN CARRIERS OF STREPTOCOCCUS EPIDEMICUS I PILOT, B HALLMAN
and D J DAVIS, J Infect Dis 47 503, 1930

Streptococcus epidemicus is found in the throats of persons during interepidemic periods. The chief habitat appears to be the crypts of the faucial tonsils. Three carriers of *S. epidemicus* had enlarged tonsils, cervical adenitis and arthritic pains. The recognition of these carriers is important because of their possible rôle in the transmission of the disease to others and particularly in the accidental infection of the udder of the cow, with subsequent explosive epidemic sore throat spread through the milk.

AUTHORS' SUMMARY

SPORADIC SEPTIC SORE THROAT DUE TO STREPTOCOCCUS EPIDEMICUS I PILOT
and D J DAVIS, J Infect Dis 47 507, 1930

The three cases were all sporadic. The source of infection was undetermined. It is possible that in such sporadic cases, carriers of *S. epidemicus* are the source.

of infection, but milk as a source cannot as yet be ruled out. Investigations bearing on possible sources are being made. Recently, we recognized *S. epidemicus* in the exudates of active otitis media, mastoiditis and cervical adenitis. The throats did not reveal acute tonsillitis. However, *S. epidemicus* may be present in the throat cultures. Some of the patients had a definite history of tonsillitis, but others were apparently well until otitis media developed. It would appear that *S. epidemicus* may also cause mild inflammations of the throat or upper respiratory passages, which may be complicated by acute otitis media and mastoiditis.

AUTHORS' SUMMARY

HERPES ENCEPHALITIS IN MONKEYS OF THE GENUS *CEBUS*, WITH OBSERVATIONS ON THE GREEN STREPTOCOCCUS. E. B. MCKINLEY and M. DOUGLASS, *J. Infect. Dis.* **47** 511, 1930.

Herpetic encephalitis has been produced in five of nine monkeys of the genus *Cebus*. The disease in its acute and subacute form closely resembles human encephalitis. The pathologic lesions are also similar to those of the human malady, except for the presence of intranuclear herpetic inclusion bodies in the ganglion cells of the cortex. The disease kills *Cebus* monkeys in from six to eleven days. Secondary invading streptococci were demonstrated in the brain of one monkey. Healthy monkeys receiving an emulsion of the brain of this monkey did not show any streptococci, either on cultivation of the brain or on inoculation of it into rabbits. Our studies indicate that the green streptococcus is not related to the virus infection in question, but that this microbe may, in occasional animals under optimum conditions, invade the central nervous system after the "soil" has been previously prepared by the virus. We therefore see no reason for attaching an etiologic relationship to the green streptococcus in such a disease as encephalitis. Difficulty has been met with in attempting to transmit herpes encephalitis from monkey to monkey. This may be due to the chance selection of refractory animals, or in some manner a neutralization of the herpes virus may occur in the brains of some monkeys.

AUTHORS' SUMMARY

EXPERIMENTAL STUDY OF DENGUE FEVER. G. BLANC and J. CAMINOPETROS, *Ann. de l'Inst. Pasteur* **44** 367, 1930.

In an extensive report of sixty-nine pages, the subjects of transmission by insects, infection of laboratory animals, immunity, properties of the virus and vaccination are discussed. It is noted that *Stegomyia*, which were maintained as long as 228 days in the laboratory, may acquire the virus from the blood of a patient up to the fifth day of the disease, they become infective after eight days and remain so for at least 174 days, or virtually for life, if kept in a temperature of 20° C. or higher. Animal experiments were successful in four genera of monkeys, dogs and rabbits were negative, and rats were doubtful, but a silent or inapparent infection occurs in guinea-pigs, monkeys and man. A firm immunity seems to be assured following an attack, but convalescent serum fails. There was no apparent cross-immunity with yellow fever serum. The virus is not preserved by drying. Bile-treated, inactive virus conferred no immunity, although repeated inoculations indicate some degree of immunity. Double vaccination was performed with (1) bile-treated (1-15) inactive virus and with (2) bile-treated (1-20) virus immunized against a heavy dose of active virus.

M. S. MARSHALL

THE GROWTH OF ANAEROBES IN RELATION TO POTENTIAL OF MEDIUM. HARRY PLOTZ and JEAN GELOSO, *Ann. de l'Inst. Pasteur* **45** 613, 1930.

Potentiometric and colorimetric studies on the changes in the ox-red potential in cultures of anaerobes are reported. Sterile broth develops an rH_2 of 7.5 at 37° C., which corresponds to that developed by dextrose alone. A limiting value of rH_2 of 5.5 is developed during the growth of anaerobes. This change in

potential is analogous to that produced by the addition of platinum black to the broth and indicates that the dehydrogenation of the dextrose is catalyzed by the growth of the micro-organisms. The results show that a rapid growth of anaerobes is obtained only when the rH_2 lies between 0 and 14

C E CLIFTON

RELATION OF BACTERIUM GRANULOSIS TO TRACHOMA P K OLITSKY, Rev internat du trachome 7 173, 1930

Up to the present, typical bodies, either intranuclear or cytoplasmic, such as characterize true filtrable virus diseases, have not been found in trachoma. Although this work is still in progress, the tentative opinion at this moment is that whenever bodies are seen, they can be shown to be bacteria, artefacts, pigment or structures similar to those found in preparations of smears taken from normal human or simian tissues.

In an experiment in which twelve macaques were employed, we have found that *Bacterium granulosis* is inactive in monkeys that are immune to the organism, but that it is specifically pathogenic in those that are normal and in those that are immune to spontaneous folliculosis. Conversely, the suspensions of tissue derived from a monkey with spontaneous folliculosis induce a follicular conjunctivitis in normal monkeys and in those immune to *Bacterium granulosis*, but are inactive in macaques that are resistant to the spontaneous disease.

CHARLES WEISS

ENLARGEMENT OF THE SPLEEN IN UNDULANT FEVER H SCHOTTMULLER, Deutsche med Wchnschr 56 1813, 1930

An enormous enlargement of the spleen in a case of undulant fever is reported. The presence of a large spleen should direct attention to the possibility of undulant fever.

HEPATITIS AND CHOLECYSTITIS, A SPECIFIC COMPLICATION OF SCARLET FEVER TOXIN H SCHOTTMULLER, Klin Wchnschr 10 17, 1931

From a clinical study of four patients and a clinical anatomic study of a fifth patient, the author concludes that the streptococcus toxin of scarlet fever is responsible for certain changes in the liver and gallbladder.

Fahr reports the anatomic study of Schottmuller's fifth patient (*Klin Wchnschr* 10 20, 1931), and describes the exudates of plasma cells, lymphocytes, histiocytes and eosinophilic leukocytes in Glisson's capsule of the liver, especially around the small bile ducts. Of special interest were the focal proliferative changes in the intima of the hepatic veins and the extensive cellular infiltrations of the entire wall. In addition, the wall of the gallbladder was diffusely infiltrated with cellular exudates. Fahr does not consider these changes specific.

EDWIN F HIRSCH

THE GROWTH FORMS AND VIRULENCE OF HEMOLYTIC STREPTOCOCCI H SCHOTTMULLER, Klin Wchnschr 10 107, 1931

Hemolytic streptococci conserved for a time on silk threads or treated with chemicals, under the influence of animal and human tissues, are so modified that they form green colonies instead of hemolytic ones. The green colony form is avirulent.

AUTHOR'S SUMMARY

A PARATYPHOUS B EPIDEMIC A PIERACH, Munchen med Wchnschr 77 2181, 1930

An explosive epidemic during which about sixty persons became infected with paratyphoid B organisms occurred in a hotel. The infections were due to food supposedly contaminated by a carrier in the kitchen. The routine examination of persons who handle food for carriers of disease is again emphasized.

EDWIN F HIRSCH

INCLUSION BODIES IN HERPES SIMPLEX HOTORI WATANABE, Zentralbl f Bakteriol **116** 38, 1930

Watanabe scarified the cornea and skin of rabbits applied herpes virus Basle III of Doerr and herpes virus Dahlem of Gildemeister and Herzberg and examined sections taken from one to seven days thereafter. Inclusion bodies that resembled Guarnieri bodies were found in the cytoplasm of the epithelial cells as well as in the connective tissue cells of the substantia propria. Inclusion bodies of the type described by W Lowenthal were not found. One colored plate is shown.

PAUL R CANNON

THE PATHOGENESIS OF TYPHOID INFECTIONS ALICE WALDMANN, Zentralbl f Bakteriol **116** 68, 1930

The author infected mice with the Breslau strain of *Bacillus enteritidis*, by subcutaneous, intravenous and enteral methods, and studied the histopathologic effects, in an attempt to determine whether or not such infections are enteral or hematogenous in origin. With the subcutaneous and intravenous methods, the principal changes occurred in the liver and spleen as nodules of histiocytic components, whereas Pyer's patches and mesenteric lymph nodes were unaffected. The latter were affected only when the micro-organisms were fed, followed later by the characteristic nodules of focal necrosis in the liver and the spleen.

The conclusions drawn are that these experiments offer no support to the views of Sanarelli, Besredka and others that the typhoid infections are primarily hematogenous with later localization in susceptible tissues, i e, the lymphoid structures of the intestinal tract. Rather, the evidence supports further the conception that the intestinal manifestations are the reactions of the lymphatic apparatus to the primary infection through the intestinal mucosa.

PAUL R CANNON

PROTECTION OF THE SPLEEN AND THE RETICULO-ENDOTHELIAL SYSTEM AGAINST SPIROCHAETA DUTTONI AND TRYPANOSOMA GAMBIENSE T H AMAKO, Zentralbl f Bakteriol **116** 280, 1930

Amaka found that the combination of splenectomy and blockade markedly reduced the resistance of mice to *Spirochaeta duttoni* and of guinea-pigs to *Trypanosoma gambiense*, the death rate being as high as 95 per cent. Compensation of the remainder of the reticulo-endothelial system occurred within four days after splenectomy. Partial splenectomy and implantation of the spleen after previous splenectomy also ensured favorable protective effects.

PAUL R CANNON

EXPERIMENTAL SYPHILIS OF RABBITS T TANI, M KAKISHITA and K SAITO, Zentralbl f Bakteriol **116** 471, 1930

The authors found a difference in susceptibility of different races of rabbits to inoculation of cultures of spirochetes of syphilis, the short-eared albino being the most susceptible. The parenchyma of the testis was the most susceptible tissue into which an injection was made, as compared with the scrotum, prepuce, skin of the back and vaginal mucosa. Infected testes, conserved in the icebox, were infectious for five days. Infection was more certain during cold weather than during warm periods. Superinfections were difficult to secure with homologous strains, but were obtained in approximately 40 per cent with heterologous strains.

PAUL R CANNON

THE ACTION OF SLIGHTLY VIRULENT TUBERCLE BACILLI IN EXPERIMENTS WITH ANIMALS P UHLENHUTH and W SEIFIERT, *Ztschr f Immunitatsforsch u exper Therap* **69** 187, 1930

Attenuated tubercle bacilli may cause extensive tuberculosis in susceptible guinea-pigs In one instance, BCG regained full virulence for guinea-pigs and rabbits after a sojourn of one and one-half years in guinea-pigs

THE INFLUENCE OF HEMATOTOXIC SUBSTANCES ON EXPERIMENTAL TUBERCULOSIS H SHIRAI, *Jap J Exper Med* **8** 457, 1930

The factor causing anemia and the inhibitory influence on the tuberculous changes do not run parallel Both hydroxylamine and glycerin cause an anemia, but they have no inhibitory influence on the tuberculous infection Pyrodine causes an anemia and also shows a marked effect on the tuberculous change The tuberculous change is not due to the anemia, but to the chemical nature of the substances From these results and those of other workers, the inhibitory action seems to be due to the hydrazine group Phenylhydrazine hydrochloric acid, methylphenylhydrazine and p-tolylhydrazine hydrochloric acid, as well as the substances mentioned, have the same effect on tuberculous infections and all have the hydrazine group as a common radical

EDNA DELVES

INFECTION OF *B ANTHRACIS* THROUGH THE GUINEA-PIG'S MUCOUS MEMBRANE K KAGAYA, *Jap J Exper Med* **8** 489, 1930

There is a marked difference in the relation of the skin and the mucous membranes to *B anthracis* Given orally, the organisms were found to penetrate the mesentery and reach one or two viscera in a short time At the same time, a few bacilli were found in the small intestines After three hours no organisms were found in the mesenteric glands or other viscera Also the percentage of organisms was greater in the large intestines than in the small After twenty-four hours, it was impossible to find any bacilli in the intestinal canal or the viscera

EDNA DELVES

Medicolegal Pathology

TRAUMA AND DEMENTIA PARALYTICA J V KLAUDER and H C SOLOMON, *J A M A* **96** 1, 1931

This article considers the medicolegal relations of trauma to dementia paralytica Each case must be considered on its own merits with respect to (1) the effect of trauma on intracranial contents, (2) the meaning of symptoms during the intercalary period and (3) the probable modification of the patient's usefulness and longevity The relation of trauma to the localization of syphilitic lesions is discussed

HISTOPATHOLOGY OF DIFFERENT TYPES OF ELECTRIC SHOCK ON MAMMALIAN BRAINS L R MORRISON, A WEEKS and S COBB, *J Indust Hyg* **12** 324, 1930

This article briefly reviews the literature as to the pathologic effect of electric shock on tissues, especially of the brain, and in addition clearly portrays the histologic changes in the brain following repeated sublethal shocks from a given quality and quantity of current Rabbits, guinea-pigs and cats were used to illustrate the effect of carefully measured amounts of different kinds of current From a histopathologic standpoint, in the cases in which repeated shocks were given with induction coil current, the dominant features in the brain were hemorrhage, demyelination, glial proliferation, excessive swelling and liquefaction

of the ganglion cells. Swelling of the oligodendroglia is one of the first signs even in cases in which a few shocks of three seconds' duration are given, death occurring in a few hours, or in those in which a single shock of from thirty to fifty seconds' duration is given, with almost immediate death. Pericapillary hemorrhage is another early sign. In older cases perivascular gliosis and demyelinated spots are seen. In animals shocked with a condenser discharge under the same conditions, which lived for from seven to seventy-two days, there were swelling and liquefaction of the ganglion cells and increased glial activity in the myelin, the ependyma and around the blood vessels, essentially the changes in shock induced by current from an induction coil. However, a limited perivascular necrosis was characteristic of this group. The series shocked with A-C current showed a greater tendency to hemorrhage, especially in the choroid plexus and the ventricles. Pericapillary extravasation of the blood, especially in the basal ganglia and the medulla, was more frequent, while lymphocytic infiltration of the pia and around the vessels was a prominent feature. Liquefaction of the ganglion cells was uncommon in the series shocked with A-current, the typical features were a greater tendency toward hemorrhage, shrinkage of the ganglion cells, a mild reaction of the glia and an absence of demyelination. Under similar conditions, the series shocked with a condenser discharge showed swollen ganglion cells, as in the induction series, the glial reaction not being as severe. In this type the myelin is not broken down but shows vacuolization and mucoid degeneration, which is more severe than in any of the other forms.

C G WARNER

TRAUMATIC ASPHYXIA W R LAIRD and M C BORMAN, Surg Gynec Obst
50 578, 1930

Although 138 cases of traumatic asphyxia have been reported heretofore in the medical literature, it is probable that the condition is more frequently found than the literature would indicate. Among the factors responsible for the morbidity of this condition are the occurrence of panics in large crowds, the collapse of large structures seating or housing large collections of people, human negligence and the desire for speed. The consequent use of machinery in industry and vehicles for rapid transportation have added materially to traumatic asphyxia. For the sake of accuracy and clarity, the authors suggest that the term traumatic asphyxia be applied to patients in whom there has been a squeezing compression of the chest and upper part of the abdomen with cessation of respiration for an abnormal length of time. They suggest that the local cyanosis occurring in an extremity following local trauma or pressure be called traumatic cyanosis, and that the rarely observed cyanosis occurring during an attack of grand mal epilepsy be termed epileptic cyanosis.

The typical syndrome described following traumatic asphyxia consists of cessation of respiration, with or without loss of consciousness, visual disturbances or blindness, extreme purplish cyanosis of the upper part of the trunk, the neck and the face, and subconjunctival hemorrhage. The invariable subconjunctival hemorrhage noted in this condition has a peculiar lozenge or wedge-shaped distribution, due to lack of supporting tissue. The cyanosis is probably essentially due to capillary and venous dilatation and engorgement as revealed by histologic studies. Multiple unsuspected fractures, especially of the thoracic vertebrae, may be associated and remain undetected, without roentgen examination. The probability of associated injuries to intrathoracic and abdominal viscera must always be remembered.

C G WARNER

THE RELATION OF SURROUNDINGS AND TRAUMA TO DIABETES F UMBER,
Klin Wchnschr 10 5, 1931

True insular diabetes does not result from psychic trauma, it results from physical trauma only when most of the pancreas has been destroyed. A psychic

or physical trauma may disclose a diabetic disposition or may aggravate an existing diabetes. These accentuations are usually insignificant.

EDWIN F. HIRSCH

ACUTE DEGENERATIVE CHANGES IN AMMON'S HORN IN FRESH GUNSHOT WOUNDS OF THE BRAIN. K. NEUBURGER, *Krankheitsforschung* 7:219, 1929

In gunshot wounds of the brain, degenerative changes and necrosis occur in Ammon's horn owing to disturbances in the circulation. These changes occur early after the injury and appear to be due to a local anemia from vasoconstriction.

NECROSIS OF UTERUS FOLLOWING INJECTION OF SOAP POWDER. W. BICKENBACH, *Med. Klin.* 26:1663, 1930

Solution of soap powder was injected into the uterus to produce abortion. On account of peritonitis, laparotomy was performed and the uterus removed about twenty-four hours after the expulsion of a fetus of 3 months. The uterus and the tubes were found to be extremely necrotic, owing it is believed, to alkali hydroxides in the soap powder.

Technical

THE NEUTRAL RED TEST IN PERNICIOUS ANEMIA. S. J. COHEN, M. J. MATZNER and IRVING GRAY, *Arch. Int. Med.* 46:979, 1930

Three cases have been reported of patients with pernicious anemia in whom injected neutral red was recovered in the gastric extractions. Previous investigators have emphasized the diagnostic value of the neutral red test in pernicious anemia. Investigators have never before been able to recover neutral red in the gastric specimens in true pernicious anemia. The value of the test for neutral red is always questionable, because the presence of the dye in the stomach may be accounted for by regurgitation of the duodenal content. A simple and rapid method for the detection of neutral red in the gastric content is described. The presence of neutral red in the gastric extractions does not in itself exclude the diagnosis of pernicious anemia.

AUTHORS' SUMMARY

THE CHOLESTEROL PARTITION OF THE BLOOD PLASMA IN PARENCHYMATOUS DISEASES OF THE LIVER. EMANUEL Z. EPSTEIN, *Arch. Int. Med.* 47:82, 1931

An added insight into the complex problem of the liver function seems to be gleaned from the determination of the total and cholesterol ester, a simple method that requires only from 1 to 2 cc of blood plasma, and that can be repeated throughout the course of the disease. Ten cases of acute, diffuse, parenchymatous damage of the liver have been studied. The cholesterol ester values in the blood plasma were found to be diminished or entirely absent, corresponding with the severity of the disease process. With the improvement in the condition the ester values rose to their absolute and relative normal proportions. This progress as revealed by the ester values paralleled in large measure the general condition of the patient and the other liver function tests. In four cases of atrophic cirrhosis of the liver, with its slow evolution, slight damage and ample regeneration, the cholesterol partition was normal. The ester values seem to offer some means of diagnosing parenchymatous damage of the liver and, when repeated during the course of the disease, some prognostic significance.

AUTHOR'S SUMMARY

THE MARCHI METHOD. DONALD DUNCAN, *Arch. Neurol. & Psychiat.* 25:327, 1931

Duncan studied the significance of so-called Elzholz bodies as brought out by the method of Marchi in human material, but especially in rats, dogs, rabbits and

cats The bodies are minute particles of myelin that stain black or brown with osmic acid They are situated between the myelin and the Schwann membrane or within the myelin and in the nodes of Ranvier The Elzholz bodies are much in evidence in secondary (wallerian) as well as in so-called primary degeneration of the nerve In the latter condition, the myelin is involved but the axon is spared Duncan concludes that normal fibers always contain some black globules and irregular areas, and that the amount of Elzholz bodies depends on the technic of the Marchi method

Fixation in formaldehyde, for instance, produces numerous artefacts, and for this reason the formaldehyde should be completely washed out in running water before the osmic acid mixture is used The Bush modification (the mixture contains 1 part of osmic acid and 3 parts of sodium iodate in 300 parts of distilled water) is considered the best and most valuable method Duncan does not consider the Marchi stain specific for wallerian degeneration The strength of the osmic acid solution is of great importance in its application

GEORGE B HASSIN

A METHOD FOR THE DIFFERENTIAL STAINING OF GRAM-POSITIVE AND GRAM-NEGATIVE BACTERIA IN TISSUE SECTIONS J H BROWN and LENA BRENN,
Bull Johns Hopkins Hosp 48 69, 1931

The authors present the following method of differential staining Stain paraffin sections in freshly filtered alum-hematoxylin (Harris) for from two to five minutes Wash in acid alcohol (3 per cent hydrochloric acid in 95 per cent alcohol) until light pink Wash in ammonia water (1 cc of aqua ammoniae in 100 cc of water) until blue Wash in water and pour on the following mixture, staining for two minutes In a small vial mix 5 drops of 5 per cent sodium bicarbonate containing 0.5 per cent phenol, with 0.75 cc of a 1 per cent (by weight) aqueous solution of gentian violet At this point it is better to proceed with one slide at a time Wash quickly with water and cover with compound solution of iodine for one minute Wash with water, blot and decolorize in 1 part ether plus 3 parts acetone, drop the solution on the slide until no more color comes off Blot and stain with rosaniline hydrochloride (0.005 Gm per hundred cubic centimeters of water) or basic fuchsin (0.1 cc of saturated alcoholic solution per hundred cubic centimeters of water) Wash in water and blot, but do not allow the section to dry Pass through acetone, decolorize and differentiate by dropping over the section a solution of 0.1 Gm of picric acid in 100 cc of acetone until the section becomes yellowish-pink This is the most critical stage of the process and should be carried out by holding the slide over a white plate or dish Most of the fuchsin should be decolorized from the tissue, but the gram-negative bacteria should remain red Pass successively through acetone, equal parts of acetone and xylene and xylene After clearing in xylene, mount in balsam

EDNA DELVES

A REAGENT FOR DEMONSTRATING FUNGI IN THE SKIN SCRAPINGS AND HAIR
T CORNBLEET, J A M A 95 1743, 1930

Several drops of water are used to dissolve a relatively large quantity of sodium sulphide crystals Equal parts of this solution and 95 per cent alcohol are mixed A precipitate develops which redissolves as distilled water is added drop by drop The reagent should be kept in a paraffin-coated, glass-stoppered bottle The alcohol removes the oil at the surface of the keratin and between the layers of scales and also gives a refractive index that makes the structures more easily visible The scales and hair should be soaked in ether to remove the oil at the surface After the material has been placed on a slide under a cover glass, several drops of reagent are added In several minutes, if the cover glass is gently tapped down, the clearing will occur more rapidly Five or ten minutes are sufficient to obtain a satisfactory clearing The microscopic picture is clear, and the vegetative structures are easily seen

EDNA DELVES

Society Transactions

PHILADELPHIA PATHOLOGICAL SOCIETY

Regular Meeting, Jan 8, 1931

BALDUIN LUCKL, *President, in the Chair*

The William Wood Gerhard Gold Medal of the Philadelphia Pathological Society was awarded to Dr Simon Fleener, director of the Rockefeller Institute for Medical Research, who addressed the Society on the subject, "Two Modern Plagues"

Regular Meeting, Feb 12, 1931

CONGENITAL PULMONIC STENOSIS WITH UNUSUAL EXTRACARDIAC LESIONS CHARLES-FRANCIS LONG

During his youth the patient was a cross-country runner. He had a strenuous four years in the British army and was on his company's soccer and boxing teams. He emigrated to America at the age of 27, passing all examinations without comment. During the summer of his thirtieth year, his skin became suddenly blue after a bath in the ocean. This color would reappear whenever he became chilled or walked against the wind. At the age of 32, he was admitted to Medical Service B of the Episcopal Hospital, complaining of the bluish color, which had been present for five months, of edema of the ankles toward nightfall, which he had observed for three months, and of urgent dyspnea and vertigo, from which he had suffered for a week. The heart was moderately enlarged to the right. The rhythm was regular. There was a rasping systolic murmur, best heard in the third interspace to the left of the sternum, it radiated to both axillae and the angle of the left scapula. There was cyanosis of the capillary type. The liver was enlarged to the level of the umbilicus. There was moderate edema of the ankles. Microscopic examination of the capillaries of the nail bed showed them to be long, tortuous and sometimes with four loops filled. The oxygen saturation of the arterial blood was normal (94.6 per cent). The dextrose tolerance test showed that at the end of two hours the blood contained 260 mg of sugar per hundred cubic centimeters, and that the urinary sugar was 1.1 per cent. The patient improved and was discharged in three weeks. During the next nine months, he was bedridden at home owing to a diarrhea which was thought to be a manifestation of colitis, there was evidence also of irritation of the cerebral and spinal motor pathways. There were periods of delirium, which would clear as suddenly as they had come. It was thought that the psychoneurologic manifestations might be evidence of a malignant endocarditis superimposed on a congenital lesion of the heart. He died in what might be described as a "typhoid state." The autopsy, as far as the heart was concerned, sustained the clinical diagnosis of congenital pulmonic stenosis. There was right ventricular preponderance. The valve measurements were: mitral, 8.5 cm, tricuspid, 9 cm, aortic, 6.4 cm, pulmonary, 3.5 cm. A probe could pass through the foramen ovale, but in the opinion of the pathologist it was not functionally patent. No ductus arteriosus was seen.

The liver weighed 2,200 Gm, was firm, a mottled brown and studded throughout with yellow umbilicated lesions, which proved to be adenocarcinoma. The pancreas was normal in size and shape, but several large hard nodules in its head were due to adenocarcinoma. There were metastases to the periportal and mesenteric glands.

EXPERIMENTALLY PRODUCED LESIONS OF RHEUMATISM V H MOON and
HAROLD L STEWART

This article appeared in the February issue of the ARCHIVES, page 190

HYPERPLASIA OF RAT AND MOUSE SKIN FROM SULPHYDRYL STANLEY P
REIMANN

Two points in the sulphhydryl theory of growth by increase in number are not generally recognized. The first is that the sulphhydryl group is the naturally occurring stimulus to cell division, and the second is that the chemical control of the well known balance between cell proliferation and its inhibition must be by way of a chemical equilibrium somewhat unique in its properties. As formulated by Hammett, reduced sulphur compounds stimulate mitosis and their semi-oxidized products inhibit this process.

To discover what would happen when sulphhydryl compounds were applied to the normal intact skin, thiocresol in various concentrations and in various mediums was painted on the skins of rats and mice. As control, cresol in the same concentrations was used on the same animals on other parts. Hyperplasias involving the epithelial cells occurred on the parts treated with the sulphhydryl compounds, whereas the parts treated with cresol remained normal. The details concerning the cellular differentiation and differential reactions between the epithelium and the underlying connective tissue will be published in detail by Hammett.

CHICAGO PATHOLOGICAL SOCIETY

Regular Meeting, Feb 9 1931

JOSEPH A CAPPS, *President, in the Chair*

VARIATION OF A BACILLUS COLI-LIKE ORGANISM W J NUNGESTER and
S A ANDERSON

An organism recently isolated from empyema of the gallbladder was studied with the purpose of observing variations. By subjecting the purified original culture to conditions intended to produce variation or dissociation, variants were obtained differing from each other with respect to form of colony, fermentation of lactose, motility and agglutinability.

The change from the original form to that of the variants was effected with some difficulty, and we are unable to state the conditions that stimulate such changes, except in a general way. On the other hand, the reversion of the variants to the parent form was effected at will. Such conditions as aging on nutrient agar or a short passage through liquid medium was sufficient to accomplish reversion in certain variants. The presence of lactose was usually necessary to bring about the reversion of the forms that did not ferment lactose.

The ease with which variation occurs in liquid mediums is a source of error in determining the carbohydrate fermentation of variants under such conditions. More accurate information concerning the fermentation of carbohydrates by variants can be obtained on Andrade carbohydrate agar on which changes from one form to another are less likely to occur than in liquid mediums.

There was no correlation of the form of the colony with fermentation of lactose. Both S and R types of colony fermented lactose. On the other hand, similar forms of colony were encountered that failed to ferment lactose.

DISCUSSION

EDWIN F HIRSCH Since so much depends on purity of the bacterial strain in these studies of dissociation, were cultures prepared by the single-organism method?

W J NUNGESTER We did not use the single-organism method because the results with such strains are the same as those with cultures purified in the usual manner

UNDIFFERENTIATED ROUND CELL SARCOMA WITH SKELETAL SARCOMATOSIS (HEMACYTOBLASTOMA?) N W ROOME

A round cell sarcoma of the ilium, with widespread skeletal, and few visceral, metastases, was reported. The patient had pain in the lower extremities, especially the left, for two years before admission, swelling in the region of the left ilium, loss of vision in the right eye and gradual loss of weight and strength. On the patient's admission to the University of Chicago Clinics a mass surrounding the left ilium and enlarged left inguinal glands were found. Roentgen examination disclosed increased thickness and density of the left ilium and of adjacent parts of the pubis and ischium. No other lesions were found at the first examination. There were moderate leukocytosis and anemia, the differential white blood cells count was approximately normal.

Treatment by Coley's toxins and x-rays resulted in slight improvement, but metastases rapidly spread into nearly all the bones of the body. The x-ray films of the skeletal metastases revealed diffuse widening of the medullary cavity, irregular changes in density of bone and slight periosteal formation of bone. There were a fluctuating fever and progressive anemia. Death occurred eight months after admission.

A huge tumor was found about the left ilium, ischium and pubis, filling the pelvis to the midline. When the tumor was cut into, the ilium was dense and thickened, the surrounding mass was coarsely trabeculated and only moderately firm, and was without bone or cartilage. The iliac lymph glands were infiltrated. All the other bones examined were massively infiltrated by tumor, causing little destruction of bone. There were tumor nodules in the pleurae, dura mater, spleen and pancreas.

The iliac tumor consisted of densely packed, irregularly arranged small "round cells" that appeared free in an irregular connective tissue stroma. In tissues treated by fixation in a solution of formaldehyde plus Zenker's solution and with Maximow's hematoxylin eosin-azure, most of the cells resembled the hemacytoblast (stem cell of the hematopoietic series) and a few cells contained neutrophil and eosinophil granules, suggesting myelocytes and premyelocytes. Most positively identified were several megakaryocytes. Certain cells with compact nuclei and acidophil cytoplasm suggested normoblasts. The cells of the metastases were less differentiated and resembled less the hemacytoblasts.

This tumor clinically resembles the "endothelial myeloma" of Ewing, but cytologically it is possibly hemacytoblastoma.

ANOMALIES OF INTESTINAL ROTATION REPORT OF TWO CASES H E HAYMOND

The first anomaly was accidentally discovered during a surgical operation (Lester R. Dragstedt) in a man 68 years of age with carcinoma of the pylorus and of the greater curvature of the stomach. Owing to the abnormality a gastroenterostomy was not done, and resection was not attempted on account of widespread metastases. A further examination was made after death. All of the small bowel, with the exception of 8 cm of terminal ileum, was behind a glistening membrane limited on the right side by the ascending colon anteriorly and the posterior parietal peritoneum posteriorly. The duodenum and the first part of the jejunum were in front of the superior mesenteric artery. The small intestine had

its own mesentery This anomaly is best explained as a malrotation of the embryonic midgut in the second stage of rotation as described by Norman M Dott It occurred when the intestines returned to the peritoneal cavity from the normal developmental umbilical hernia and passed anterior to the superior mesenteric artery, thus forming a sac from the embryonic mesentery of the ascending, and the right half of the transverse colon

The second patient with intestinal anomaly was a boy, aged 16 years, who had had intermittent attacks of severe vomiting since he was 2 days old At operation (Lester R Dragstedt) the cecum was found behind the stomach in the upper left quadrant, and the ascending colon and terminal ileum were wound around the base of a short mesenteric pedicle in such a manner as to produce obstruction of the upper part of the jejunum At the operation a twist of the small intestine of 120 degrees was found and corrected, and the cecum was fixed in the right lower quadrant The postoperative course was uneventful Eleven and one-half months after operation, he had had no recurrence of symptoms and had gained approximately twenty pounds (9 Kg) in weight This anomaly is explained as an excessive rotation and abnormal fixation of a previous floating ileocecal segment of the embryonic midgut

The complete report will be published in *Surgery, Gynecology and Obstetrics*

THE COPPER, IRON AND ANTITRYPSIN CONTENTS OF POTENT EXTRACTS OF THE ROUS CHICKEN SARCOMA No 1 DAVID ROSBASH and ARTHUR LOCKE

Freshly prepared extracts of Rous chicken sarcoma contain, on an average, 0.38 mg of copper and 1.16 mg of iron per gram of their nitrogen content, amounts nine times as large as those that characterize similarly prepared extracts of the pectoral muscles of control, nontumor-bearing hens The metal-carrying fraction of the sarcoma extracts is concentrated, together with the tumor-inducing principle, by acid fractionation

Saline extracts of the pectoral muscles of normal hens appear to be devoid of antitryptic potency Similarly prepared extracts of Rous sarcoma tissue have an inhibiting action on trypsin approaching that of the blood serum in dilutions of equal nitrogen content The antitryptic activity is concentrated, together with the copper content and the tumor-inducing principle, by acid fractionation

Extracts of Rous sarcoma are not inactivated by cyanide They behave, in this respect, like the "anaerobic" enzymes of the classification presented in a preceding paper It is suggested that the "aerobic" enzymes of this classification, which are readily inactivated by cyanide, may be similarly inactivated by antitrypsin Possibly the resistance to cyanide and the increased metal contents of the extracts of sarcoma indicate an increased anaerobic enzyme content, and the activity of the extracts may depend, in part, on their capacity (1) to suppress the aerobic processes, and (2) to supplement the anaerobic processes, of the cells contiguous to the area into which the injection has been made in such a way as to urge these cells gradually to convert into more wholly anaerobic, tumor cells

CARCINOMA OF THE JEJUNUM GEORGE MILLES

Less than 200 carcinomas of the small intestine have been recorded In large series of postmortem statistics, about 3 per cent of all carcinomas of the intestine have been found in the small bowel

Like malignant growths elsewhere in the intestines, carcinomas of the small intestine manifest themselves clinically by obstruction and intussusception and by metastases, which in about half of the cases reported occurred early and almost entirely in the liver

A Russian laborer 33 years of age, noticed progressive loss of weight for a year and epigastric pain after meals for a month One week after the onset of this pain, anorexia and vomiting increased his discomfort to such an extent that he sought relief in a hospital During the month preceding admission he lost 20 pounds (9 Kg) and during the entire year 43 (19.5 Kg) A moderate

emaciation was noted, and a mass estimated to measure 6 cm in diameter was palpated in the midepigastrium. There were 3,100,000 red blood cells per cubic millimeter of blood and 70 per cent hemoglobin, and the stomach fluids contained a total of 3 degrees of acid, but no free acid. The roentgen examination demonstrated an annular deformity of the pylorus. With a clinical diagnosis of carcinoma of the stomach, an operation was undertaken to relieve the obstruction. The liver was invaded by carcinomatous nodules, and the pylorus of the stomach was involved in a large mass which could not be resected. An anterior gastro-enterostomy was performed. The patient left the hospital after twelve days. He failed to recover his weight and strength, and the discomfort in the abdomen increased. After four months, vomiting became so marked that he was able to retain only small quantities of milk. He entered the Research and Educational Hospital of the University of Illinois, markedly emaciated, weak and pale. The abdomen protruded moderately and through the thin wall could be palpated the enlarged liver with its irregular, nodular edge and a separate mass in the right epigastrium. The hemoglobin was reduced to less than 20 per cent, and the red blood cells to 2,000,000 per cubic millimeter, there were many nucleated and irregular red cells. The leukocytes numbered 12,250 per cubic millimeter, of which 85 per cent were polymorphonuclear leukocytes. The gastric fluids contained 28 degrees of acid, but no free acid, and occasional traces of blood. Blood was found in the feces. The serum albumin was reduced to 2.59 per cent, the serum globulin was unchanged. Death occurred one month after admission and one and one-half years after the onset of symptoms. The peritoneal cavity contained 600 cc of clear fluid. Opposite the healed abdominal incision were adhesions binding the intestines and the liver to the anterior abdominal wall. The liver weighed 5,230 Gm and contained many umbilicated nodules, varying in color from tan to yellow, and as large as 3 cm in diameter. The intervening liver substance was dark brown. The site of the gastro-enterostomy was obscured by surrounding adhesions, and the pylorus of the stomach, the duodenum, the jejunum and the medial half of the pancreas formed a mass which was disentangled with some difficulty. There was a thickening in the posterior wall of the jejunum close to the gastro-enterostomy. The stomach contained about 100 cc of bile-stained fluid. The mucosa was pale, and both the pyloric orifice and the opening made by gastro-enterostomy were patent. About 1 cm distal to the latter in the jejunum was a superficial raised ulceration, 3 cm in diameter. Sections from this and from the liver presented adenocarcinoma. The failure to find carcinoma in the stomach or in the pancreas led to the conclusion that the mass in the jejunum was the primary adenocarcinoma. The tumor cells definitely resembled goblet cells.

Book Reviews

ANATOMIE UND PATHOLOGIE DER SPONTANERKRANKUNGEN DER KLEINEN
LABORATORIUMSTIERE, KANINCHEN, MEERSCHWEINCHEN, RATTE, MAUS
Edited by RUDOLF JAFFE, Berlin Price, 98 marks Pp 832, with 270 partly
colored illustrations Berlin Julius Springer, 1931

This book is the product of twenty-eight contributors who summarize what is known about the spontaneous diseases of the rabbit, guinea-pig, rat and mouse. The object of the work is (1) to assist the investigator working with these animals in determining whether conditions he may observe in them in the laboratory are the results of his experiments or are due to spontaneous diseases—an urgent problem that may arise at any time—and (2) to stimulate careful observation and study of the natural diseases of these animals on account of their inherent scientific interest as well as their bearing on experiments.

The vast amount of material on which the book is based has been gathered by laborious search of the literature as well as by systematic observations in various German institutes, particularly the Institut für Vererbungsforschung an der Landwirtschaftlichen Hochschule (Berlin-Dahlem), which has served as a depot for distributing material to the various contributors. That all recorded observations, often hidden in articles on other topics, have been included would be more than one can expect. And that the field of the book has been covered completely by the work that has been done up to this time is of course also out of question. But the book does meet the requirements that reasonably may be placed on a book of its kind at present. The hopes of the editor that in time the results of further work may warrant a new edition should receive encouragement.

The book is divided into two parts, special and general. The special part deals with the organs—it is essentially a pathologic anatomy—and covers 565 pages. By way of introduction to each organ system, the peculiarities in the normal anatomy of each species are described. The general part is devoted to the bacterial and parasitic diseases of the four species in question, carbohydrate metabolism and tumors. The bacterial and parasitic diseases are reviewed thoroughly. Chapters planned for the consideration of lipid, mineral and pigment metabolism had to be omitted on account of lack of suitable material. The section on spontaneous tumors covers its field exhaustively, and the American work, notably that of Maude Slye receives full and adequate attention. At the ends of the section are lists of references. The illustrations are satisfactory.

The book will be of help and interest to all who work scientifically with the rabbit, guinea-pig, mouse and rat. There is frequent need for a book like this in every laboratory where studies are made on these animals.

DIE GLOBULINE. By DR. MONA SPIEGEL-ADOLF. Volume IV. Handbuch der
Kolloidwissenschaft. Edited by Prof. Wolfgang Ostwald. Price, 33 marks.
Pp 452. Dresden. Theodor Steinkopff, 1930.

The importance of the proteins as subjects for research in both the physical and the biologic sciences has resulted in a literature on proteins that is as varied as it is extensive. The task of collecting this literature, therefore, is extremely difficult since it carries the reader through many different types of journals ranging from theoretical chemistry and physics to clinical medicine. One consequently finds that practically all books on proteins tend to consider these important and interesting substances from the chemical and physicochemical points of view, and to ignore, or else dismiss with only a few meager references, the

important evidence bearing on the behavior and structure of protein obtained from immunologic studies. In the present volume, Dr Spiegel-Adolf considers not only the chemical and physical but also the biologic and medical aspects of the subject. Her training in pathology and medicine, together with her extensive researches on the physical chemistry of the proteins, makes her especially fit to discuss these compounds from this comprehensive point of view. The result is a volume of great interest not only to colloid chemists but to physicians and biologists interested in following the important advances being made in the chemistry of protein.

Although this book deals with the globulins, and more specifically with the serum globulins and the vegetable globulin edestin, it contains many hundreds of references covering the entire field of the chemistry of proteins. Chapter 1, on the chemistry of the globulins, deals with the various kinds of globulins, their preparation and their chemical and physical properties. Chapters 2 and 3 deal with the reactions of globulins with alkalis and with acids. In chapter 4, the author discusses the solubilities of the globulins in neutral salt solutions and the chemical and physical properties of such solutions. Chapter 5 deals with the reactions of globulins with salts of heavy metals, inorganic colloids and such biologic colloids as the lipoids. Chapter 6, on globulins in biology and medicine, deals with quantitative methods for the determination of globulins, fluctuations of globulin content in health and in disease and immunologic properties of the globulins. The comprehensive manner in which the author has covered the field of the globulins together with the full and impartial discussion of the subjects presented makes this monograph invaluable to all who are interested in this class of proteins. It should also prove especially useful as a source of references to the older and important papers on the general chemistry of protein as well as to those dealing more specifically with the globulins themselves.

UEBER DAS PROBLEM DER BOSARTIGEN GESCHWULSTE. EINE EXPERIMENTELLE UND THEORETISCHE UNTERSUCHUNG. By PROF. DR. LOTHAR HEIDENHAIN. Volume 2. Price, 42 marks. Pp 207, with 229 illustrations. Berlin: Julius Springer, 1930.

Heidenhain, whose first volume on the same subject was reviewed in the *ARCHIVES* (7:378, 1929), affirms that carcinoma and sarcoma are always caused by a transmissible and infectious agent which is enclosed within the tumor cells. By a rather simple procedure of digestion of human neoplasms, given in detail in the previous review, he "frees" the agent from the malignant cells and the formless detritus resulting from the digestion containing the carcinogenic substance is then injected in small amounts into the thigh, the liver or the peritoneum of mice; this, Heidenhain asserts, leads to the inauguration of a new growth somewhere in the rodent's body.

Previous to Heidenhain's work no one was able to transfer cancer from man to animal. And, what is more, material freed from living malignant cells, as a rule, failed to induce a cancer in another animal of the same species.

The results presented by Heidenhain in no way disprove the "orthodox" teaching just mentioned. The percentage of the alleged positive results in his experiments is very small (about 7 in the first series and about 11 in the present volume), and it is most likely that the tumors in the mice are spontaneous, although Heidenhain quotes the names of a few German pathologists who informed him that spontaneous tumors are almost unheard of in the Teutonic mouse.

In brief, the present study by Heidenhain is no more than a continuation of that already published, since the same material and the same experimental methods were used. The monograph abounds in illustrations which together with the legends occupy 133 of 207 pages of the book. Unfortunately, the excellent plates are by no means a proof that the malignant condition found in the mice resulted from the inoculation of the "detritus." Moreover, the arguments brought forward by Heidenhain in defense of his thesis are rather unconvincing.

RECENT ADVANCES IN THE STUDY OF RHEUMATISM By FREDERIC JOHN POYNTON, M D, F R C P (LOND), Physician, University College Hospital, Senior Physician, Hospital for Sick Children, Great Ormond Street, and BERNARD SCHLESINGER, M A, M D (CAMB), M R C P (LOND), Physician to the Children's Department, Royal Northern Hospital, Physician to Out-patients, Hospital for Sick Children, Great Ormond Street Price, \$5 50 Pp 313, with 25 illustrations Philadelphia P Blakiston's Son & Company, 1931

This book discusses the nomenclature, causation, morbid anatomy and treatment of "rheumatic diseases" in the light of recent developments. The first part deals with the nomenclature and the industrial aspects of the diseases. The second and largest part is devoted to "acute rheumatism," its causation, morbid anatomy, relation to tonsillitis, the allergic factor, electrocardiography and treatment. The rheumatism of childhood and the convalescent home treatment for rheumatic children receive detailed consideration. The third part deals with "chronic rheumatism"—bacteriologic investigations, morbid anatomy, metabolic changes, focal infection and treatment. The senior author is known in the history of the investigation of rheumatism for his bacteriologic researches in conjunction with Dr Payne. The book gives a comprehensive and sympathetic picture of the results of the modern investigations of the nature of rheumatism. The recent American work receives full attention. The specific streptococcal theory, the multiple streptococcal theory, the allergic theory, the role of focal infection, the anatomic changes and other aspects of the rheumatic problems are subjected to judicial and helpful review. The book will appeal to all who are interested in the advancement of knowledge concerning the rheumatic infections.

AN INTRODUCTION TO PRACTICAL BACTERIOLOGY A GUIDE TO BACTERIOLOGICAL LABORATORY WORK By T J MACKIE, M D, D P H, Professor of Bacteriology, University of Edinburgh, and J E MCCARTNEY, M D, D Sc Third edition Price, \$3 50 Pp 421 New York William Wood & Company, 1931

The first edition of this work appeared in 1925. The book was designed to set forth "as briefly as possible the essential methods and data relating to practical bacteriology." First come brief chapters on the biology of microbes, immunity in relation to bacteriology, the microscope, cultural and staining methods, animal inoculation, immunologic methods, water, milk and antiseptics. Chapters 9 to 23 deal with the characters of the disease-producing microbes and the diagnosis of infections by laboratory methods. There are no illustrations, except a few diagrams, no references and no discussion of the historical aspects of microbiology. There is inconsistency in that the proper names of microbic species occur now in ordinary type, now in italics. The book is a compact and up-to-date guide for the beginning worker in practical microbiology.

TEXT-BOOK OF GYNECOLOGY By ARTHUR H CURTIS, M D, Professor and Head of the Department of Obstetrics and Gynecology, Northwestern University Medical School, Chief of the Gynecological Service, Passavant Memorial Hospital, Chicago Cloth Price, \$5 Pp 380, with 222 original illustrations Philadelphia W B Saunders Company, 1930

Pathologists, especially those who are concerned with the pathologic anatomy and histology of the female genital organs, will be interested in this textbook. It embodies a refreshingly concise presentation, based on personal experience, "of all that the author believes is vital in [clinical] gynecology." The illustrations are original, and it is to those of the microscopic appearances in various processes and the interpretation of them by the author that the attention of practical pathologists is directed especially. The author has a firm, firsthand grasp of general pathologic principles, and his gross and microscopic descriptions and illustrations are admirable. To the pathologist who must deal with gynecological material in the laboratory and often away from the clinic, this book will be of great help because it describes and illustrates, simply but adequately, the important morphologic appearances in their clinical setting.

Books Received

SOCIETÀ INTERNAZIONALE DI MICROBIOLOGIA, SEZIONE ITALIANA ATTI DEL
SECONDO CONGRESSO NAZIONALE DI MICROBIOLOGIA Pp 271 Milano
Istituto Sieroterapico Milanese, 1930

DIE SEXUELIEN ZWISCHENSUFEN Von Richard Goldschmidt, Dr Phil Nat
et Med H C, Professor und Direktor am Kaiser Wilhelm-Institut für Biologie in
Berlin-Dahlem Price, 45 marks, bound, 46 90 marks Pp 528, with 214 illustra-
tions Berlin Julius Springer, 1931

ABSTRACTS OF THESES Science Series, volume 7, Ogden Graduate School of
Science Submitted to the Graduate Faculty of the University of Chicago for
the Degree of Doctor of Philosophy, September, 1928—June, 1929 Pp 484
Chicago University of Chicago Press, 1931

RECENT ADVANCES IN FORENSIC MEDICINE By Sydney Smith, M D,
M R C P, D P H, Regius Professor of Forensic Medicine, University of Edin-
burgh, and John Glaister, Jr, M D, D Sc, J P, Barrister-at-Law, Inner Temple,
Professor of Forensic Medicine, The Medical Faculty, University of Egypt, Cairo,
and Medico-Legal Consultant to the Egyptian Government Price, \$3 50 Pp 194,
with 66 illustrations Philadelphia P Blakiston's Son & Company, 1931

REPORT OF THE MEDICAL RESEARCH COUNCIL FOR THE YEAR 1929-1930
Price, 2 shillings, 6 pence Pp 138 London His Majesty's Stationery Office,
1931

DILT AND THE TEETH AN EXPERIMENTAL STUDY Part 2 A Diet and
Dental Disease B Diet and Dental Structure in Mammals Other Than the
Dog Medical Research Council, Special Report Series, no 153 By May Mel-
lanby Price, 2 shillings, 6 pence Pp 93, with 28 illustrations London His
Majesty's Stationery Office, 1930

IODINE SUPPLY AND THE INCIDENCE OF ENDEMIC GOITRE Medical Research
Council, Special Report Series, no 154 By J B Orr Price, 4 pence Pp 18
London His Majesty's Stationery Office, 1931

UNDULANT FEVER WITH SPECIAL REFERENCE TO A STUDY OF BRUCELIA
INFECTION IN IOWA National Institute of Health Bulletin, no 158 By A V
Hardy, C F Jordan, I H Borts and G C Haidv Price, 25 cents Pp 89
Washington, D C Government Printing Office, 1931

DIE HISTOGENESE EKTO-MESO-DEPMALER MISCHGESCHWULSTE EIN
BEITRAG ZUR FRAGE DER ORGANISATORENWKUNG (SPEMANN) BEIM PATHO-
LOGISCHEN WACHSTUM Von Prof Dr Paul Schurmann, Dr med Hans Pfluger
und Zahnarzt Dr Wilhelm Norrenbrock Price, 11 50 marks Pp 94, with 79
illustrations Leipzig Georg Thieme, 1931

A SYSTEM OF BACTERIOLOGY IN RELATION TO MEDICINE Medical Research
Council Volume 6 (Immunity) Cloth Price, per volume, 1 pound, 1 shilling,
net London His Majesty's Stationery Office, 1930 (May be obtained from
the British Library of Information, 551 Fifth Avenue, New York)

TEXT-BOOK OF PATHOLOGY By Robert Muir, M A, M D, Sc D, LL D,
F R S, Professor of Pathology, University of Glasgow, Pathologist to the Western
Infirmary, Glasgow Price, \$14 Pp 872, with 501 figures New York and
Toronto Longmans, Green & Company, 1930

STUDIEN UBER DIE ENTSTEHUNG UND DEN VERLAUF DER LUNGENKRANK-
HEITEN Von Dr N Ph Tendeloo, o o Professor der allgemeinen Pathologie
und der pathologischen Anatomie, Direktor des pathologischen Instituts der
Reichsuniversitat, Leiden Zweite umgearbeitete und vermehrte Auflage Paper
Price, 26 marks Pp 219, with 6 illustrations Munich J F Bergmann, 1931

CHLOROFORM CONTENT OF THE BRAIN FOLLOWING ANESTHESIA*

ALEXANDER O GETTLER, PH D

AND

HYMAN BLUME, BS

NEW YORK

The problem of determining the chloroform content of the brain following anesthesia suggested itself to us as a direct result of a medicolegal case, involving our aid in the solution of the same

A woman, aged 35 years, died in a doctor's office. An autopsy, performed by Dr Charles Norris, Medical Examiner of the city of New York, disclosed perforation of the posterior vaginal vault, with the presence of about 300 cc of blood in the peritoneum, but no evidence of peritonitis. Parts of the liver, brain and lungs were submitted to one of us (A O G) for chemical analysis. Chloroform was found present. The amount in the lungs was 52 mg in 1,000 Gm. The estimated amount of chloroform in 1,000 Gm of brain was 156 mg. These results were compared with the values found in our series of cases in which death occurred during chloroform anesthesia or following the administration of chloroform with suicidal or homicidal intent (see table 1).

The figures in table 1 indicate that the brain of a person sufficiently anesthetized for a minor operation contains between 120 and 182 mg of chloroform in 1,000 Gm of brain tissue. In the case under discussion, the chloroform content of the brain was 156 mg in 1,000 Gm of tissue. This figure falls within the amount needed for complete mild anesthesia. An excessive amount of chloroform was not present (An excessive amount ranges between 372 mg and 480 mg—cases 1 to 7). The cause of death in the case under discussion was therefore given as hemorrhage following an incomplete abortion.

The doctor in whose office the woman was found maintained that he administered no chloroform, that he performed no operation of any kind, that the woman came to him to be treated and died before he could attend her. In order to prove or disprove the doctor's contention, the determination of the chloroform content of the brain and lungs

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was of vital importance. Chloroform was present in the organs of the woman. Where was it administered? In the doctor's office or somewhere else? If administered at some other place, how soon after coming out of the anesthesia did the woman feel well enough to walk? The cells continually adding the organism of chloroform, how much chloroform could remain in her brain on her arrival at the doctor's office? These are the questions we were asked to answer.

On looking over the figures of table 1, we find that in the case of persons anesthetized for minor operations, the chloroform content is between 120 mg and 182 mg in 1,000 Gm of brain. The case in question had 156 mg, indicating that the deceased person was under the influence of chloroform and therefore not able to walk, hence, the chloroform must have been administered on the premises.

TABLE 1—*Chloroform Content of the Brain in Cases in Which Death Involved the Administration of Chloroform*

Case	History	Mg Chloroform in 1,000 Gm Brain
1	Suicide by inhalation	432
2	Suicide by inhalation	480
3	Suicide by inhalation	410
4	Suicide by inhalation	390
5	Homicide by inhalation	372
6	Homicide by inhalation	384
7	Homicide by inhalation	374
8	Anesthesia for abortion, shock	162
9*	Anesthesia for abortion, hemorrhage	60
10	Anesthesia for operation on tonsils, shock	136
11	Anesthesia for minor operation, shock	135
12	Anesthesia for minor operation, shock	145
13	Anesthesia for minor operation, shock	120
14	Anesthesia for minor operation, shock	122
15	Anesthesia for abortion, shock	182
16†	Anesthesia for minor operation, shock	70

* Patient came out of anesthesia, died of hemorrhage.

† Patient died from shock during administration of chloroform, was not fully anesthetized.

It seemed important to investigate this problem further by means of experiments on animals, to determine how soon after chloroform anesthesia the individual is again able to walk normally, and how much chloroform is present in the brain at varying intervals of time after the administration of chloroform. The present report is based on this work.

TECHNIC OF EXPERIMENTS ON ANIMALS

Ten dogs were used in these experiments. After being tied to the animal board, they were anesthetized with chloroform, the open mask method being used. They were kept in a state of surgical anesthesia for definite periods. The mask was then removed, and the animals were allowed to recover spontaneously. Dog 6 was not allowed to recover, but was killed by excessive administration of chloroform. In dogs 5 and 7, the trachea was clamped while they were fully anesthetized. In order to investigate the chloroform content of the brain at various stages of recov-

ery, the dogs were killed at stated intervals, as indicated in the chart. Painless death was obtained by injecting morphine and then exposing and clamping the trachea. Autopsy was then performed. The brain and lungs were removed, weighed and placed in the icebox in sealed containers until the analysis was started.

Method of Analysis—The brain and lungs, when ice-cold, were ground up, and quickly placed in a 500 cc distillation flask, about 100 cc of water was added and also a little tartaric acid, enough to make the mixture acid in reaction. The material was then subjected to steam distillation, a long, well cooled condenser and an adapter being used. The receptacle for collecting the distillate, a 300 cc Erlenmeyer flask, contained about 10 cc of ice-cold, acidified (HCl) water and was packed in ice. The tip of the adapter reached into the ice-cold water contained in the receptacle for distillate. With these precautions, there was no loss of chloroform during distillation. Our experiments have proved that, if 250 cc of distillate is collected, all of the chloroform in the tissues will have passed into the distillate. The distillate was well mixed, measured, stoppered and kept cold, 5 cc portions of this distillate were taken for the colorimetric determination.

Colorimetric Estimation of Chloroform in Distillate—The materials necessary for the colorimetric estimation of the chloroform in the distillate were chemically pure pyridine (colorless), 20 per cent sodium hydroxide solution, and the standards to be described.

Chloroform Standards One gram of pure chloroform was weighed out. This was done by placing a little more than 1 Gm of chloroform into a weighing bottle with a ground glass stopper, allowing the chloroform to evaporate spontaneously and weighing from time to time (with weighing bottle stoppered) until the weight of the chloroform in the bottle was just 1 Gm. This gram of chloroform was then dissolved in about 900 cc of water contained in a 1 liter volumetric flask, 5 cc of hydrochloric acid was added, and finally enough water was added to bring the total volume to exactly 1 liter. The whole was thoroughly mixed. Precautions were taken to avoid evaporation of the chloroform during the transfer. This solution contained 1 mg of chloroform in each cubic centimeter. From this stock solution, a series of weaker standards were made, having the following chloroform values: 0.5 mg in 1 cc, 0.1 mg in 1 cc, 0.01 mg in 1 cc, 0.005 mg in 1 cc, 0.0025 mg in 1 cc. These standards do not keep, new standards were made for each set of determinations.

Procedure Into five clean, dry, 50 cc test tubes were pipetted 5 cc portions of the five standards containing, respectively, 0.5 mg, 0.1 mg, 0.01 mg, 0.005 mg and 0.0025 mg of chloroform per cubic centimeter (see preparation of standards). Into a similar test tube was pipetted 5 cc of the distillate. To each of the tubes, 5 cc of chemically pure (colorless) pyridine and 10 cc of 20 per cent sodium hydroxide solution were added. The contents of each tube were mixed and the tube loosely corked to avoid evaporation. The tubes were placed in a boiling water bath for exactly one minute and then quickly cooled by running water, 20 cc of water was added to each tube, and the contents were mixed. Of the series of standards, the one that matched the color of the unknown closest was used as the standard and read against the unknown in the colorimeter.¹

Calculation

$$\frac{\text{Standard}}{\text{Unknown}} \times \frac{\text{Value of standard used in milligrams of chloroform}}{\text{milligrams of chloroform in grams of tissue used}} \times \frac{250}{5} \times 1.087 \left\{ \begin{array}{l} \text{correction for per-} \\ \text{centage of recovery} \end{array} \right\}^1$$

¹ Gettler, A. O., and Blume, Hyman. Chloroform in Brain, Lungs and Liver, Quantitative Recovery and Determination, *Arch Path* **11** 554, 1931.

RESULTS OF ANALYSES

The results, which are charted in table 2, indicate the following (all values calculated to 1,000 Gm of brain tissue)

An animal killed by excessive administration of chloroform had 551 mg of chloroform in the brain. Animals killed while in chloroform anesthesia had 270 mg and 284.6 mg of chloroform in the brain. Animals that were allowed to recover from the anesthesia showed a rapid decrease in the chloroform content of the brain, i. e. after 34 minutes, 51.3 mg, after 50 minutes, 33.3 mg, after 65 minutes, 32.6 mg, after 95 minutes 23.6 mg, after 102 minutes, 10.6 mg, after 186 minutes, 5.2 mg, and after 190 minutes, 0.16 mg.

TABLE 2—*The Rate of Disappearance of Chloroform from the Dog's Brain During Recovery from Anesthesia*

Dog	Body Weight, Kg	Weight of Brain, Gm	Time in Minutes							Mg of Chloroform in Brain at Death	
			To Anesthetize	Until First Signs of Recovery	Until Placed on Floor	At Which Hind Legs Were Still Ataxic	Until Dog Began to Look Normal	Until Death	Between Normal Appearance and Death	In Entire Brain	Calculated† to 1,000 Gm of Brain
1	8.5	80	15	6	8	19	*	34	*	4.10	51.3
2	5.7	75	15	5	17	30	35	50	15	2.50	33.3
3	6.3	69	15	4	6	15	30	65	35	2.25	32.6
4	6.9	70	15	6	10	75	*	95	*	1.65	23.6
5	9.4	82	12	5	10	35	45	102	57	0.87	10.6
6	5.2	52	15	5	6	30	42	186	144	0.27	5.2
7	11.3	60	15	4	8	25	30	190	160	0.01	0.16
8	7.6	60	15	Trachea clamped while completely anesthetized						16.20	270.0
9	6.5	65	15	Trachea clamped while completely anesthetized						18.50	284.6
10	7.6	68	7	Killed by excessive administration of chloroform						37.70	551.5

* Morphine injected while animal was still ataxic

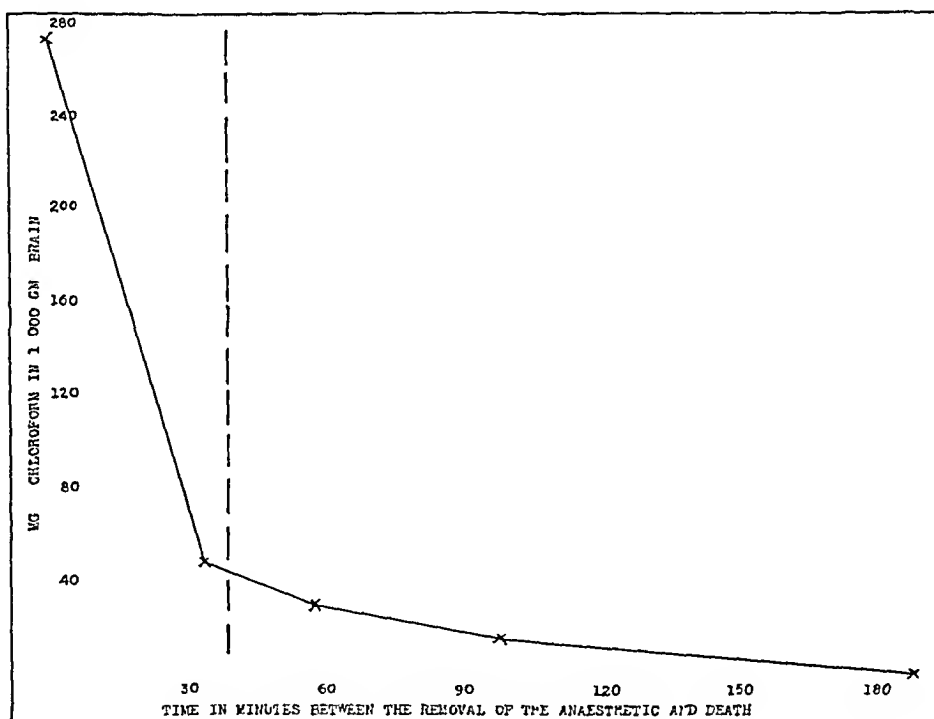
† Chloroform content of human brain is best reported on 1,000 Gm basis, in order to facilitate comparison the chloroform in the dogs' brains was also calculated to 1,000 Gm portions

It was between thirty and forty-five minutes before the dogs looked normal and could walk normally. Dog 1 probably was killed just as it was beginning to return to normal. It had 51.3 mg of chloroform in the brain. Fifteen minutes after dog 2 seemed normal, it had 33.3 mg of chloroform left in the brain, calculated to 1,000 Gm of tissue. Thirty-five minutes after dog 3 seemed normal, it had only 32.6 mg. This is an indication that from fifteen to thirty minutes after the animal seems normal, the brain contains only from 30 to 35 mg of chloroform in 1,000 Gm.

The lungs in some of the dogs were also analyzed. The values are not charted. We found that in the recovery stage the lungs contained only from 33 to 50 per cent of the amount of chloroform found in the brain.

The chloroform content of the brain of the deceased person in question was 156 mg in 1,000 Gm of tissue. On the basis of the determined figures, we hold that The woman at the time of her death was still under chloroform anesthesia and not in a condition to walk. With 50 mg of chloroform or thereabouts per thousand grams of brain tissue, she would have shown the first indication of normal coordination. If it took her only from fifteen to thirty minutes to get to the doctor's office, her brain should contain at the most from 30 to 35 mg of chloroform.

The various points determined in our experimental work are vividly brought out by plotting milligrams of chloroform in 1,000 Gm of brain



against time in minutes, as in the accompanying chart. Attention might be called to the following points brought out by the plotted curve. When animals which have been in full chloroform anesthesia are allowed to recover, the chloroform content of the brain drops rapidly. In our experiments, in 34 minutes it dropped from 278 mg to 51.3 mg, in 58 minutes it was down to 33 mg. From this point on, the chloroform kept decreasing, but more slowly. After 188 minutes, only 27 mg of chloroform in 1,000 Gm were left (average values for dogs 6 and 7). In the chart, the vertical dash line at the 40-minute interval indicates the point at which the animals first began to appear normal again. Eighteen minutes after the animals seemed normal, the brain contained only 33 mg of chloroform in 1,000 Gm.

SUMMARY

A dog killed by the excessive administration of chloroform contained in the brain 551.5 mg of chloroform in 1,000 Gm of tissue. Animals while fully anesthetized with chloroform contained in the brain 270 mg and 284.6 mg in 1,000 Gm of tissue. When an animal was in the stage of recovery, the chloroform content of the brain dropped very rapidly during the first 34 minutes, so that only 51.3 mg in 1,000 Gm of brain tissue was left. From then on, the chloroform content decreased more slowly, and after 190 minutes there was only 0.16 mg of chloroform present in 1,000 Gm of brain. Animals appeared normal again after 40 minutes. At this time they probably had about 45 mg of chloroform in 1,000 Gm of brain. Fifteen to thirty minutes after the animals seemed normal the brain contained 35 to 30 mg of chloroform in 1,000 Gm. In the stage of recovery, the lungs contained much less chloroform than the brain.

LEIOMYOSARCOMA OF THE PLEURA

REPORT OF A CASE ^{*}

LLOYD CATRON, B S

CHICAGO

Reports of primary sarcoma of the pleura are not numerous. Robbins,¹ in 1908, described a large fluid-containing sac filling the left side of the thoracic cavity in a woman, it was lined by a thickened and nodular pleura, which on microscopic examination was seen to be composed of a vascular tissue containing many spindle-shaped and irregularly shaped cells. Peripherally these cells invaded the subpleural adipose tissue. Metastases were present in the right lung and in the liver. From the literature Robbins summarized reports of ten instances of primary pleural sarcoma in which he believed the diagnosis reasonably certain. In 1908, Mehdorf² reported a myxomatous fibrosarcoma in a 43 year old woman. The firm, well encapsulated tumor weighed 3,270 Gm and filled the right side of the thoracic cavity. Microscopically there were many spindle-shaped cells in a connective tissue network, and myxomatous changes were found. There were no metastases. Pallasse and Roubier,³ in 1915, described an enormous malignant lipoma of the pleura in a 75 year old woman, and in a 51 year old woman a fibrosarcoma weighing 2,500 Gm. They classified tumors of the pleura as benign, mixed and malignant, and grouped the latter into diffuse and circumscribed types.

More recently, Nevinny⁴ found in the right side of the thoracic cavity of a 43 year old woman a tumor 18 cm in diameter. It contained large, blood-filled spaces, and was enclosed in a well defined capsule. Microscopically, most of the cells were seen to be spindle-shaped. No metastases were present. Nevinny considered the tumor a primary giant cell sarcoma of the pleura. MacMahon and Mallory,⁵ in 1928, described in detail a slowly progressing fibrosarcoma of the right side in a 71 year old white man. The thickened and nodular pleura lined a large

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^{*} From the Department of Pathology of the Cook County Hospital

1 Robbins, W B. Boston M & S J **158** 691, 1908

2 Mehdorf, Robert. Virchows Arch f path Anat **193** 92, 1908

3 Pallasse, E, and Roubier, C. Ann de méd **3** 243, 1915

4 Nevinny, Hans. Mitt a d Grenzgeb d Med u Chir **40** 277, 1927

5 MacMahon, H E, and Mallory, G K. Am J Path **4** 387, 1928

sac containing 2,200 cc of bloody fluid. Microscopically, cells varying from spindle shape to round and polymorphous, with single or multiple nuclei and many mitotic figures, were embedded in a collagenous connective tissue stroma.

In the cases of primary pleural sarcoma which have been mentioned and in those cited from the literature by these authors and by Grabow,⁶ most of the tumors were grossly of either of two types. In one of these, the pleura was nodular and thick and enclosed a large sac filled with bloody fluid, in the other, there was a single, firm, usually enormous tissue mass. The two types were of approximately equal occurrence. The microscopic structure was not uniform, and most of the tumors were classified according to cell morphology.

The present report describes a histologically malignant primary tumor apparently originating from the smooth muscle of the pleura, which has been shown by Baltisberger⁷ to be present in superficial and deep layers of definite bundles, as well as in the walls of blood vessels.

REPORT OF CASE

Clinical History—On May 13, 1930, an 83 year old white widow, Austrian, without occupation, was admitted to Cook County Hospital. In the examining room a diagnosis of arteriosclerosis was made, and the patient was placed in the medical service of Dr. McMullen. Although apparently not acutely ill, she was confused, and no history was obtainable, aside from the statement that she had suffered from pain in the left side of the chest for two months.

Physical examination revealed a greatly emaciated, extremely restless, elderly woman. The temperature was 99.6 F, the pulse rate, 76, the respiratory rate, 22, and the blood pressure 210 systolic and 100 diastolic. The thorax was long and narrow. The expansion of the chest was somewhat diminished on both sides. Many harsh rhonchi were heard over both lungs. The position and borders of the heart seemed normal, and a loud systolic murmur was best heard at the base. The liver was palpable 2 cm. below the costal margin, and the abdomen was distended, especially in the lower half. The arteries of the extremities were tortuous and hardened. No signs of intrathoracic tumor were elicited, and the patient's condition was diagnosed as hypertensive heart disease with generalized arteriosclerosis.

The patient continued to be restless and confused and was occasionally violent. Her temperature varied between 97 and 98 F until a terminal rise to 102.6 on June 8. She died on June 9, twenty-seven days after her entrance into the hospital and about three months after the onset of her illness.

Autopsy—Seven hours after death autopsy was performed by Dr. R. H. Jaffe. The body was 154 cm. long and weighed 76 pounds (34.5 Kg.), with the abdomen four fingerbreadths below the level of the chest, and midline fat practically absent. The liver weighed 950 Gm., was adherent to the diaphragm, and extended 10 cm. below the xiphoid process and 3.5 cm. below the costal arch. The diaphragm was at the level of the sixth rib.

6 Grabow. Berl. klin. Wchnschr. **47** 1625, 1665 and 1707, 1910.

7 Baltisberger, Wilhelm. Ztschr. f. Anat. u. Entwicklung. **61** 249, 1921.

The left side of the thoracic cavity was partly obliterated by fibrous adhesions. The upper lobe of the left lung was crepitant in its superior two-thirds and at the inferior tip, and the apex was much distended. The remaining part of this lobe and the entire lower lobe were airless and markedly compressed by a large, firm tumor mass, to which the lung was adherent in an area, 10 by 3 cm, over the lower lobe and by small fibrous tags near the hilus. The rounded tumor measured 22 cm vertically, 18 cm in transverse diameter, and 8 cm antero-posteriorly. Its surface was firm, and smooth, except for a few slightly projecting nodules. Some of these at and near the superior pole of the mass, the largest 15 mm in diameter, were a homogeneous deep red, others near the hilus of the lung, the largest 3 mm in diameter, were pearly white. There was a moderate



Fig 1—Leiomyosarcoma of the pleura (picture taken from the Kaiserling specimen) *a*, soft yellowish-gray tissue with openings into a cavity, *b*, light yellow nodule

number of dilated small blood vessels, with occasional deep red spots ranging in size from that of a pinpoint to that of a pinhead. Elsewhere the surface was grayish white. The tumor was covered by thickened pleura, which bore numerous fibrous tags. On the cut surfaces (fig 1) the tumor was seen to be composed of three roughly spherical nodes, the largest of which measured 15 by 9 by 7 cm, separated by smaller nodules. The surfaces of two of these nodes were firm, light gray and homogeneous, with numerous rounded orifices 1 mm or less in diameter. In an area, 5 by 2 cm, in the lowermost node (fig 1 *a*), the surfaces were softer and yellowish gray, with openings up to 6 mm wide which led into an irregularly shaped cavity crossed by trabeculae of yellowish gray tissue. The superior, largest node was softer than the others, and was composed of a network

of interwoven gray and reddish-brown tissue. A nodule, 3 cm by 1 cm, was soft and light yellow (fig 1 b).

The visceral pleura over the left lung was smooth, except for a few small fibrous tags and the adhesions to the surface of the tumor. The bronchial mucosa was injected and thickened, the cartilaginous rings were calcified, and the bronchi were diffusely dilated and contained mucoid pus. The intima of the pulmonary arteries was smooth. The hilus and the mediastinal lymph nodes were soft, small and black. The right lung was distended, and in the right lower lobe was a fibrocaseous nodule 6 mm in diameter. There were no tumor metastases in the lungs or elsewhere.

The other conditions found at autopsy were as follows: severe sclerosis of the coronary arteries, moderate atheroma of the aorta and of the peripheral arteries, dilatation of the heart and degeneration of the myocardium, arteriosclerosis of the kidneys, brown atrophy of the liver, atrophy of the spleen, cholelithiasis, nodose goiter, atresia of the external uterine os and marked cachexia.

Microscopic Examination—Tissue from the three nodes and from the light yellow nodule was taken for microscopic examination. The specimen had been fixed in Kaiserling's solution. Frozen sections were stained with sudan III and hematoxylin, hematoxylin and eosin, and with the Bielschowsky-Maresch silver impregnation. Paraffin sections were stained with hemalum and eosin, van Gieson's stain, Heidenhain's iron hematoxylin, Mallory's phosphotungstic acid and hematoxylin, Mallory's aniline blue, and Weigert's elastic stain.

The tumor of the left pleura consisted of interwoven bundles of tissues of two types. In one type the cell contained a large ovoid nucleus with delicate chromatin network. The cytoplasm, yellow with van Gieson's stain and red with Mallory's connective tissue stain, consisted of homogeneous, narrow bands prolonged from the nuclear poles or of delicate projections from the nuclear periphery. The other tissue was a fibrillar connective tissue, with deeply staining collagen bands, between which were long, flattened, darkly staining nuclei. Some parts of the tumor consisted almost wholly of cells of the first type, in a delicate connective tissue stroma. Such was the structure immediately adjacent to the pleura, about the blood vessels, and in irregularly distributed foci throughout the growth. In other regions the proportions of the two types were almost equal. Finally, there were parts in which the connective tissue was dominant, with only sparsely scattered cells of the first type. Such an arrangement was present immediately peripheral to necrotic parts of the tumor.

The mass was well encapsulated by the pleura, which was from 1 to 3 mm thick. In this capsule, near the hilus of the left lung, the pleura contained distinct bundles of smooth muscle fibers that apparently passed rather abruptly into the large cells of the tumor. Between the visceral pleura of the left lung and the capsule of the tumor were a few strands of fibrillar connective tissue. The thickest parts of the capsule were composed of dense hyaline tissue.

Throughout the mass were numerous thin-walled small blood vessels. The elastic stain revealed only a very few fine, deep blue fibers in the walls of these vessels. Peripheral to some, the cells of the tumor were flattened and formed concentric whorls. Some of the vessels contained mixed thrombi, adjacent to these there were extravasation of blood, a moderate diffuse infiltration by lymphocytes, polymorphonuclear leukocytes and plasma cells and pyknosis of the nuclei of the tumor cells.

In disseminated regions there was complete necrosis, as in the small yellow area on the cut surface seen grossly. Numerous small foci of retrogressive changes were present, alternating in some parts with well stained areas that were



Fig 2—Area of great cellularity. Note the variation in size and shape of the nuclei of the blastomatous muscle fibers. Hemalum-eosin, $\times 800$

adjacent to blood vessels, and thus producing a peculiar patchy appearance. Where these retrogressive changes had occurred, in some places the nuclei were pale, the chromatin was indistinct, and there were fine fat droplets between the cells, in other parts there were polymorphonuclear leukocytes and lymphocytes, and finally, in regions nearly necrotic, the connective tissue was hyaline, and few nuclei were visible.

The left lung was not infiltrated by the tumor, but the alveoli near the periphery were markedly compressed, with some atelectasis. In the perivascular and peribronchial lymphatics were focal accumulations of polymorphonuclear leukocytes, and a few of the alveoli were filled by these cells. The bronchial epithelium was desquamated, the nuclei were pyknotic, and the cytoplasm was granular. The mucosa was densely infiltrated by lymphocytes. These cells were also grouped in perivascular and interstitial accumulations. The cartilage of the bronchi was calcified. The walls of the arteries and of the veins were thickened, and the capillaries were dilated. Mononuclear phagocytes contained small granules of dark brown pigment. There was moderate pigmentation of the lung with coal dust, and a few of the alveolar septums were clubbed.

The histology of the tumor was as follows. Nuclei were centrally placed in the large tumor cells (fig 2). Most of these nuclei were ovoid or fusiform, but many appeared rounded or irregularly shaped, and some were slightly constricted in the central portion. In many of the cellular regions mentioned they were very large, in other parts they were smaller and narrower. All contained a fine chromatin net with coarse dots at the points of the crossing of the threads. There were no nucleoli. In most parts of the tumor a distinct nuclear membrane was present. There were very few mitotic figures. The cytoplasm was in most parts fusiform, extending from the two nuclear poles as homogeneous bands, but in some places it formed fine processes extending in various directions from the nucleus. Some of the cell tips were branched. No fibrils were visible in these cells, and the Bielschowsky silver impregnation revealed no intervening reticulum. The stroma was typical collagenous connective tissue. In some regions collagen formed closely adjacent broad bands, in other parts there were only fine fibrils about the large tumor cells. The connective tissue nuclei were larger and in some places more numerous than is usual.

COMMENT

Clinical examinations during the month that the patient was hospitalized did not lead to a diagnosis of intrathoracic tumor. The signs often associated with such a growth, such as dyspnea, visible protrusion of the wall of the chest and enlargement of the superficial veins, were not apparent. The clinical diagnosis of arteriosclerosis was confirmed at autopsy, at which the cause of death was found to be severe sclerosis of the coronary arteries. The pleural tumor was therefore incidental.

Primary pleural sarcomas of all sorts are rare, and I know of no report of a primary malignant smooth muscle tumor. In the present instance there were connective tissue fibers and nuclei throughout the mass, so that the term *fibroleiomyosarcoma* might be thought appropriate. Cells of other than connective tissue type were so dominant, however, and the signs of malignant changes in the nuclei of the connective tissue cells were so scarce that the term *leiomyosarcoma* seems preferable.

Little can be said concerning the immediate cause of this tumor. The absence of an adequate clinical history makes it doubtful that pleuritis preceded the tumor. Such a process was observed clinically in the patients whose pleural tumors were reported by Nevins⁸ and by Kidd and Habershon.⁸ The relation of such an inflammatory lesion to the formation of tumor is obscure.

The presence of a well defined capsule, the absence of metastases and the scarcity of mitotic figures, as well as the clinically benign nature of the tumor here described, may seem to demand a diagnosis of leiomyoma. But the heterotypic morphology of the growth, the decided variation in the size and shape of the nuclei of the tumor cells, and the marked anaplasia of these nuclei in many cellular regions speak for a histologically malignant tumor. It is well known that many malignant growths that attain a large size locally produce no metastases. The absence of metastatic foci in the bodies of persons with huge pleural sarcomas is pointed out by Nevins in his own case and in the five from the literature that he considered of similar nature.

SUMMARY

A massive leiomyosarcoma of the pleura of the left side of the chest of an 83 year old white woman is reported and discussed.

The literature of primary pleural sarcomas is briefly reviewed. No report of a malignant smooth muscle tumor has been found.

⁸ Kidd, P. K., and Habershon, S. H. *Tr. Path. Soc. London* **49** 15, 1898.

FLEXNER-JOBLING RAT CARCINOMA

EFFECT OF FEEDING LIVER AND MUSCLE ON GROWTH OF TUMOR¹

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The marked beneficial effect of the administration of liver to patients with pernicious anemia has stimulated the administration of this substance to patients with other pathologic conditions, including malignant diseases¹ However, before these reports on the effect of the administration of liver to patients who had carcinoma were made, we had started the first of our series of experiments to ascertain the effect of liver on the growth of the Flexner-Jobling rat carcinoma The results of these experiments were very definite and were reported² However, the experiments did not disclose whether the effect observed was due to the liver specifically or to the diet high in protein Accordingly, other experiments subsequently were performed in which the effect of the feeding of muscle also was observed

There is some evidence that the liver might have a more or less specific relationship to the development of malignant conditions An enormous amount of work has been done in an attempt to discover a relationship between lipid metabolism and malignancy Sufficient positive data have been secured to make the quest for this relationship interesting The liver is a most outstanding organ concerning which an important function in regard to lipid metabolism can be postulated The hypothesis has been advanced from the embryonic point of view, based on the fact that the liver is relatively large in the fetus, that the liver might be of significance in malignant conditions Therefore, as has been said, in accordance with this consideration,³ liver has been administered to patients with carcinoma

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¹ From the Division of Experimental Surgery and Pathology, the Mayo Foundation

¹ Middleton W S The Erythropoietic Response of the Various Anemias to Liver Therapy, J A M A **91** 857, 1928 Strisower, R Die appetiterregende Wirkung der Liberdiaet bei Krebs, Wien med Wchnschr **77** 1754, 1927 Tuchfeld, H Pierre Marie'scher Osterarthropathie hypertrophiante pneumique, Wien med Wchnschr **77** 815, 1927

² Caylor, H D The Influence of Liver Feeding on the Rate of Growth of Flexner-Jobling Rat Carcinoma, Proc Staff Meet, Mayo Clin **3** 454, 1928

³ Howitt, J R Liver Extracts in Treatment of Malignant Disease, Nature **118** 263, 1926

PROCEDURE

The Flexner-Jobling⁴ rat carcinoma was the tumor used in all experiments. The recipients were white rats of known age. The animals were inoculated, by means of the trochar method,⁵ with bits of living tumor tissue. Small groups of rats of the same age and size were inoculated at one time. Following the successful transplantation of the tumors the rats were divided into three groups, one group to be fed liver, one group a ration high in protein (fresh muscle) and one group the common maintenance ration, as a control. All of the animals were kept in the same room in cages of the same type. They were all fed one of two maintenance rations: either the ration suggested by Steenbock,⁶ or a diet composed of bread and milk twice weekly, combined with oats and an occasional feeding of dog biscuit. Fresh liver was placed each day in the cage of the animals that were to be fed liver in addition to the regular ration, and fresh, uncooked muscle, in addition to the regular ration, was given to the group that was to be fed a ration high in protein. The liver and muscle were usually consumed.

The ages of the animals at the time of inoculation with the tumor varied from 23 to 120 days. Under ether anesthesia, transplantation was made into the subcutaneous tissue of the back of each animal. Measurements of the two transverse dimensions of the tumor were made with calipers when the tumor was sufficiently large (usually about 0.5 cm) to permit correct measurement. These data were recorded, with the weight of the animal, changes in the general condition of the animal and changes in the tumor. The two dimensions of a tumor, namely, a and b (these measurements were usually at right angles to each other), being known, the volume of the tumor was assumed to be given approximately in arbitrary units by the formula $a \times b (a + b)$. Twenty-six control rats, twenty-nine rats that were fed liver and fifteen rats that were fed muscle were observed.

RESULTS

Early in the experiments it became evident that there were differences in the three groups of animals. These differences were evident in regard to the length of life after inoculation with the tumor and in regard to the volume of the tumor at the time of death.

The arithmetical averages of the numbers of days between inoculation of the animals with the neoplasm and the deaths of the animals were as follows: in the control group, 113 days, in the group that was fed liver, 90 days, and in the group that was fed a ration high in protein, 88 days. When these data were plotted on logarithmic probability paper, it was found that the curves for the group of animals that were fed liver and the group fed a diet high in protein were below the curve for the control group.

4 Flexner, Simon, and Jobling, J. W. Studies upon a Transplantable Rat Tumor Originally Regarded as a Sarcoma, Probably a Teratoma from Which an Adeno-Carcinoma Developed, Monographs, New York, Rockefeller Institute for Medical Research, 1910-1912, vol. 1-4, pp. 1-50.

5 Mann, F. C. Attempts to Obtain Transplantable Tumor in the Higher Species of Animals, *J. Cancer Research* 4: 331, 1919.

6 Steenbock, H. A Satisfactory Ration for Stock Rats, *Science* 58: 449, 1923.

The volume of the tumor at the time of death was almost always larger in the group of animals fed liver than in the control group. The ratio of the average volume of the tumor in the first group (fed liver) to the average volume of the tumor in the control group was 1.35:1. The results, plotted on logarithmic probability paper, revealed that the curves for the volume of the tumor in the control animals and in the animals fed on a ration high in protein, at the time of death, were almost always below the curve for the volume of the tumor in the animals fed liver.

It is noteworthy that after ulceration of the tumor there was usually diminution in the size of the lesion. This was probably due to the reduction of the internal pressure in the tumor with the loss of substance of the carcinoma. In our experience with the Flexner-Jobling carcinoma, usually, when the lesion reached a size of from 1.5 to 2 cm. there was necrosis in the center of the tumor, and as the growth increased the region of degeneration in the center increased, so that after about sixty days the neoplasm was composed of a thin rim of living growing tumor tissue, whereas the bulk of the tumor was composed of carcinoma cells in various stages of degeneration.

It was furthermore worthy of note that in the group of rats fed liver there was no regression of the tumor in any rat, in contrast with the fact that in five of the fifteen rats fed fresh muscle and in seven of the twenty-six rats fed the control ration the tumors regressed.

SUMMARY AND CONCLUSION

From these data it is apparent that, following the transplantation of Flexner-Jobling rat carcinoma, the animals fed fresh liver or muscle as an adjunct to their regular ration lived for fewer days than did the animals fed the usual laboratory ration. At the time of death the volume of the tumor was larger in the animals fed liver than in the control group and the group given the ration high in protein. The number of days between the inoculation of the rat with the tumor and the ulceration of the growth was greater for the control group than for the rats fed liver. What element was supplied to the diet of the animals by the liver that apparently stimulated the growth of the tumor is not known although the demonstrated stimulative effect of cholesterol and lecithin would suggest that these substances might have been responsible. It seems likely that the addition of liver or of a ration high in protein to the regular ration of the rats that were inoculated with the tumor increased the nutriment for the growth of the tumor which probably should be considered much as a parasite. Although these observations were made in animals and with a transplanted tumor that cannot be considered the same as a spontaneous neoplasm growing in man it would seem worth while to proceed very cautiously in the administration of liver to patients with carcinoma.

DISSEMINATED VENOFIBROSIS (PHLEBOSCLEROSIS)

ITS CLINICOPATHOLOGIC SIGNIFICANCE *

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Venous lesions, particularly venofibrosis, have, we believe, a far greater claim, than do hemorrhagic diatheses, to the facetious title of "step-child of pathology," bestowed on the latter by E. Frank.

Venofibrosis (phleboscлерosis) is not mentioned in Delafield and Prudden's "Textbook of Pathology" or in that of MacCallum. Beattie and Dickson mention merely that phlebo(veno)sclerosis is similar to thrombophlebitis and is said to occur in syphilis and gout. The classic German textbooks on pathology, Kaufmann's and Aschoff's, devote but a few lines to the subject. In the monumental pathologic encyclopedia edited by Henke and Lubarsch four pages are given to discussion of phleboscлерosis.

When one turns to the clinical significance of this condition, the information to be gleaned from the standard textbooks on clinical medicine is even more meager than that found in books on pathology. Thus Barker's "Monographic Medicine" dismisses the subject with a few lines. This applies to textbooks, as well as to monographs. Only in the "Traité de médecine et de thérapeutique" by Gilbert and Thoinot, is considerable space devoted to the description of the lesions of the veins and to the discussion of phleboscлерosis—by Widal and Bezançon—in the most complete article on the subject.

INCIDENCE OF THE CONDITION

Judging by the paucity of the information contained in books, as well as in the current literature, one would naturally regard the condition as a clinical curiosity, we do not think it is. A series of 24 cases occurring within eight months in a small service of a 175 bed hospital after Dr. Hauswirth had called attention to disseminated venofibrosis in a young man aged 31, and diagnosed his terminal condition as portal thrombovenosclerosis has convinced us that the condition cannot be rare. A search of the literature has corroborated our impression as to the relatively infrequent recognition of the condition.

* Submitted for publication Nov. 8, 1930.

There are two interesting publications one by Martin and Meakins¹ and the other by Martin and Tull² Martin and Meakins "emphasize the fact that phlebosclerosis is of far greater frequency than is generally supposed, and more especially in young adults, without associated arteriosclerosis" They reported 31 cases, the ages of the patients ranging between 18 and 45, but especially between 20 and 30 In their opinion phlebosclerosis existed in 60 per cent of all patients examined by them The pathologic and clinical data will be described further on Martin and Tull found this condition in 12 of 30 children from 4 to 15 years of age This opinion as to the relative frequency of the condition is shared by Widal and Bezançon³ and Souques and Janvier⁴ Several cases were seen by Dr Hauswirth in clinics other than our own

PATHOLOGIC DATA

The lesion that we have been studying for the past few months has been referred to in the literature—when at all mentioned—under several names hypertrophy of the veins, endophlebitis, hyperplastic phlebitis and phlebosclerosis Neither phlebitis nor hyperplastic phlebitis seems to us a happy choice for the name of the lesion, since there does not appear to be any evidence of an inflammatory reaction in any of the veins that we have studied so far, the word "hypertrophy" would be a much better term were it not for the fact that, clinically, it conveys little information, we liked the term "venosclerosis" because the veins so affected feel exactly like sclerosed blood vessels, but had to abandon it because it gives the idea of a condition similar to arteriosclerosis-atheromatosis with calcification We have decided to adopt the word "venofibrosis," notwithstanding that it carries with it the suggestion of there having been at one time an inflammatory process, although we have no morphologic evidence of it Believing, as we do, that the process is primarily replacement fibrosis of the muscle of the media, as well as subendothelial fibrosis of the intima, we feel that the word "venofibrosis" is preferable

Of the earlier investigators, Lobstein, who introduced the term "phlebosclerosis," thought it parallel in its histomechanics to arteriosclerosis Sack⁵ believed phlebo(veno)fibrosis, like arteriosclerosis, to be due to nutritional disturbance, with primary weakening of the media, according to him, the latter is followed by the dilatation of the

1 Martin, C F, and Meakins, J C *Am Med* **10** 611, 1905

2 Martin, C F, and Tull, J *Arch Pediat* **25** 191, 1908

3 Widal and Bezançon, in Gilbert and Thoinot *Traite de medecine et de therapeutique*, Paris, Masson & Cie, 1927, vol 1, p 689

4 Souques and Janvier, quoted by Widal and Bezançon (footnote 3)

5 Sack, E *Virchows Arch f path Anat* **112** 403, 1888

lumen (phlebectasia) and finally, by the proliferation of connective tissue, resulting in thickening of the intima. Sack believed that phlebo(veno)fibrosis occurs most frequently in the lower extremities, owing to greater changes in the hydrostatic pressure, our experience agrees with this observation.

Fischer⁶ claimed that phlebo(veno)fibrosis is analogous to arteriosclerosis, and, like Koester and his pupils, he regarded it as an inflammatory process, he claimed to have found regularly some inflammatory changes in the walls of the veins, but admitted that there was no proliferation of elastic fibers (seemingly an argument against the similarity of phlebofibrosis and arteriosclerosis). Fischer pictured the inflammatory process as spreading from the vasa vasorum toward the intima, the elastic tissue resisting the inflammation the longest, the intima is protected by the internal elastic lamina, and when it is finally attacked, its involvement is focal—phlebofibrosis *circumscripta*. Fischer believed that the process occurs most frequently after the age of 35, and that the etiologic factors are largely those responsible for arteriosclerosis—"alcohol, gout, and syphilis."

Mehnert, quoted by Barach,⁷ regarded veno(phlebo)fibrosis as either primary or secondary, the former shows weakening of the wall of the vessel and connective tissue proliferation of the intima, while the latter is due to a diffuse venous stasis.

Keya, also quoted by Barach, believed venofibrosis to be due to an abnormally increased functional demands on the veins by muscular effort, the thickened intima being a partial manifestation of the hypertrophic process, unlike Joies, however, he regarded the splitting of the elastic lamellae as a passive process.

Simmonds⁸ did not regard phlebo (veno) fibrosis as an inflammatory process and assigned the etiologic rôle to lead, gout and syphilis, according to him, the lesion comprises degenerative changes in the intima and hypertrophy with degenerative changes of the media. Simmonds stressed the fact that none of his seven cases showed any inflammatory picture, although they were observed in different stages of the disease, none of his sections showed any cellular infiltration, scar tissue or periphlebitic changes (this, of course, militates, according to Benda, very strongly against the syphilitic nature of the lesion).

The opinions at our disposal are obviously far from unanimous. On the one hand, we have the opinion of Simmonds, Sack, Weitzmann, Mehnert, Neumann, Manchat, Zwingmann, Dmitijeff and others that venofibrosis is not an inflammatory lesion, on the other hand, the opinion

6 Fischer, B. Beitr. z. path. Anat. u. z. allg. Path. **27** 494, 1900

7 Barach. Beitr. z. path. Anat. u. z. allg. Path. **50** 71, 1911

8 Simmonds. Virchows Arch. f. path. Anat. **207** 360, 1912

of Fischer, Koester and his pupils, who believed that it is Some of the adherents of the theory that the lesion is noninflammatory regard venofibrosis as a reparative process, while Sack and his school expressed the belief that it is a nutritional disturbance Other authors regard the process as similar to arteriosclerosis, while some deny this As to the etiologic factors some favor infection (syphilis), others see the true cause in chemical poisons (e g, lead), while still others look on it as a result of a metabolic disorder (e g, gout)

Of the recent writers on the subject, Benda⁹ seemed inclined to regard phlebo(veno)fibrosis as a senile atrophic process and one not parallel to arteriosclerosis

Our own observations on over thirty veins can be summarized as follows Vessels are always small, never dilated We have never seen any inflammatory changes, such as cellular infiltration, scar formation, edema, necrosis, etc, frozen sections have never shown fatty droplets, nor have we ever seen calcium deposits The histologic changes seem to be uniform and constant The very earliest changes seem to be the loss of the endothelium and the hyalinization of the denuded surface There is a marked hyperplasia of fibrous connective tissue particularly in the media, and to a lesser extent in the intima, the latter very frequently shows irregularly thickened projections into the lumen Often both the media and the intima are so involved that it is difficult to determine the limitations of the layers, a striking feature is the appearance of small muscle bundles surrounded and separated by enormously thickened connective tissue septums, at times even the individual muscle cells are thus surrounded and separated, the entire media in a preparation stained either by van Gieson's method or by Mallory's aniline blue method, having a striking alveolar appearance resembling, architecturally, the isolated appearance of islets of hepatic parenchyma surrounded by connective tissue septums as in Laennec's cirrhosis of the liver

Most frequently the entire circumference of the vein is involved, but occasionally (especially in advanced cases) there is a very pronounced irregularity of the fibrotic process, so that there seem to be localized bulgings into the lumen, and one part seems to be several times as thick as another (venofibrosis *circumscripta s nodosa*) The lesions are equally pronounced in the vasa vasorum

CLINICAL DATA

To begin with, we feel that there are several objections to the view that venosclerosis (fibrosis) is a process similar to arteriosclerosis

⁹ Benda, C, in Henke and Lubarsch *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1924, vol 2, pp 829-833

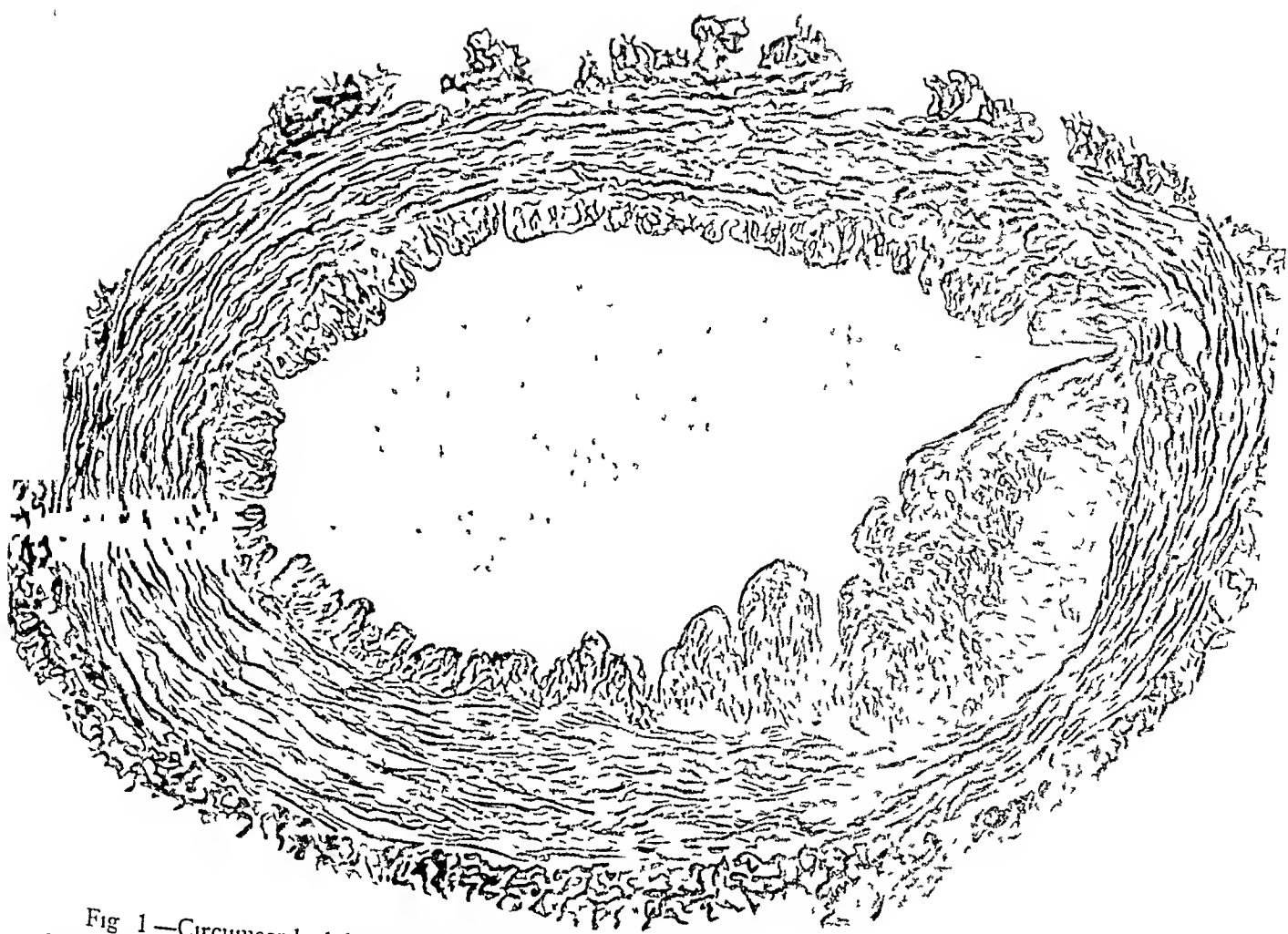


Fig 1—Circumscribed bulging of the wall of a vein, caused by marked local proliferation of fibrous connective tissue (venofibrosis circumscripta) The condition was observed in a case of gastric ulcer occurring in a man, aged 34 Mallory's aniline blue stain was used

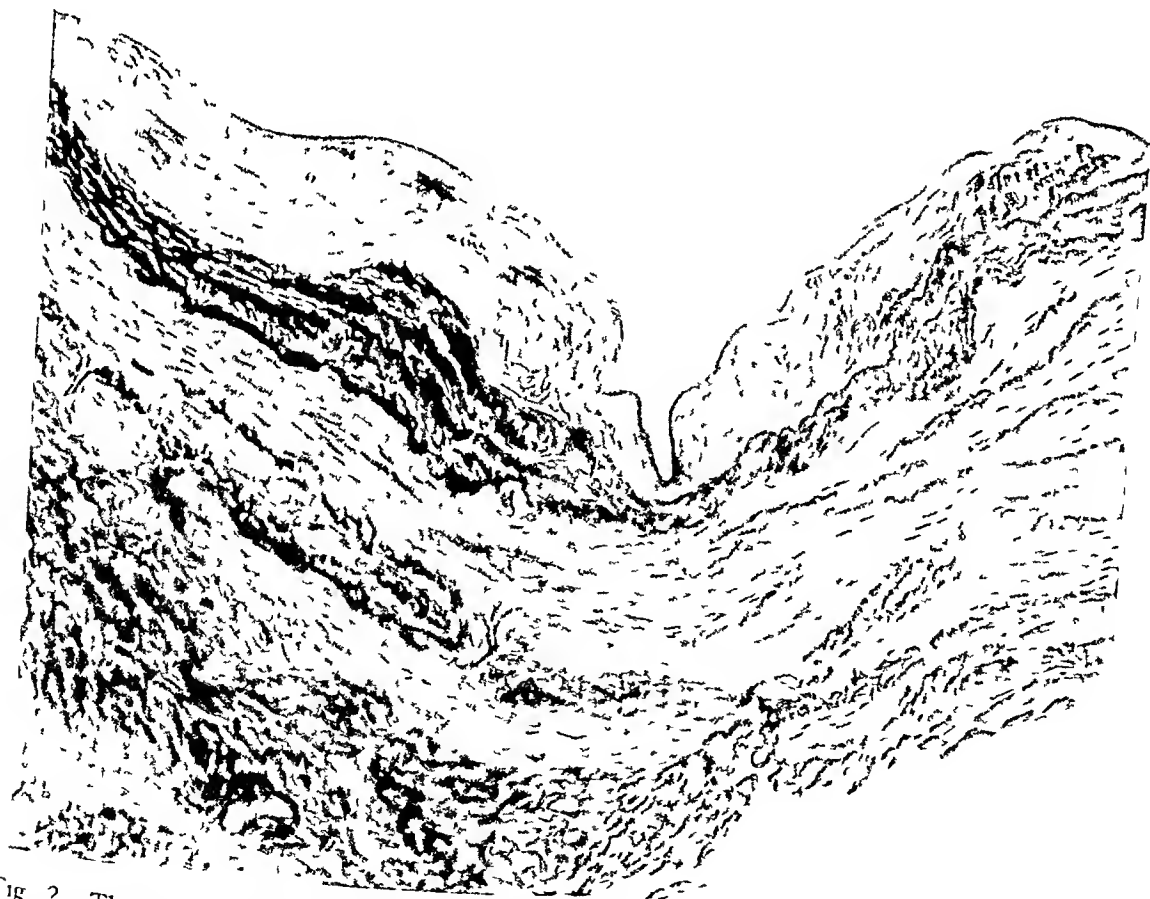


Fig 2—Thickened intima, uniformly structureless and denuded of endothelium marked fibrosis between the thickened intima and the media The condition was seen in a superficial vein of a leg in a case of duodenal ulcer, operated on ten years previously Mallory's aniline blue stain was used

Were the two processes similar or parallel to each other, venofibrosis should be met with much more frequently than it has been in the past (In spite of our belief that the rarity of the condition is much more imaginary than real—a belief based both on previous experience and on the articles of Martin and Meakins and Martin and Tull—we consider that venofibrosis is rarer than arteriosclerosis, even allowing for the general oversight of the condition during the general physical examination. Who examines veins unless there are varicosities?) The patients observed by us, as well as by the author mentioned, were younger men—under 40 (Martin and Meakin's patients were largely under 30)—than those in whom diffuse arteriosclerosis is encountered. We have, however, found venofibrosis in three arteriosclerotic patients, one was a man aged 45, with a history of familial arteriosclerosis, and the other two were men aged 23 and 26, juvenile arteriosclerotic patients, one of whom had a family history of the condition. It is reasonable to suppose that were the two processes parallel (etiologically, as well as pathologically) veno(phlebo)fibrosis would have been observed particularly by some of the investigators (whose name is legion) who have produced arteriosclerosis artificially, whether by the mechanical method of Klotz or by feeding large amounts of cholesterol (Chalatow, Anitschkow, Saltykow) or of proteins (Newburgh and March, Nuzum and others). The histories of our patients do not point to lead, gout or syphilis, but frequently show an association with peptic ulcer. A few of our patients have been operated on for that condition, and, strange to say, these patients not only do not show any cardiac hypertrophy, but possess hearts demonstrably smaller than normal.

We believe venofibrosis is overlooked largely because it develops painlessly, slowly and insidiously, without edema (except in the cases of portal venofibrosis and thrombosis) and symptomlessly, unless inflammatory changes develop subsequently. Unless the veins are examined as methodically and regularly as are the arteries, venofibrosis will continue to be overlooked. It may be of interest to relate that since we called attention to our first two cases the house staff has repeatedly recognized the condition. *A priori* one should expect venous lesions to be much more common than arterial ones, thin-walled vessels carrying from the tissues all their waste, as well as carbon dioxide, subjected to more mechanical strain, easily involved in injuries and inflammatory reactions—they seem to have escaped clinicopathologic studies.

We find venofibrosis a disseminated condition present in superficial or deep parts of the body never confined to one organ to one extremity or to one side—in other words venofibrosis has impressed us as a bilateral symmetrical condition. The veins impart a sensation

of hard cords, small, mobile and smooth, then caliber is diminished—a sensation diametrically opposite to that offered by a varicose vein. When one is palpating a fibrosed vein near the malleoli, it is necessary to have the patient manipulate his foot—extending it and flexing it on the leg—in order to be sure that one's fingers are not feeling a tendon, so closely do the fibrosed veins and tendon simulate each other in the sensation they impart and in their color, a surgeon has exposed a fibrosed vein in performing biopsy and was uncertain, even then, whether the structure lying on his grooved director was a vein or a tendon.

A striking feature—usually the first to attract one's attention—is a longitudinal niche in the skin corresponding to the location of a fibrosed vein, this is particularly pronounced over a bone where the vein seems to groove the bone, and presents a depression along its entire course.

There are no subjective symptoms accompanying venofibrosis, not even when, as in one of our cases (of thrombo-angitis obliterans), the vein of the "well" leg (i. e., as yet without symptoms) is actually fibrosed, thrombosed and canalized. Our study of a case of thrombo-angitis obliterans has shown us that a superficial vein from the arm presented the usual characteristics of fibrosis, a superficial vein from the leg without any clinical abnormalities, subjective or objective, with normal oscillometric determination and normal reaction to the Aldrich test, was completely thrombosed, and the thrombus was canalized, neither the vein from the arm nor the vein from the well leg showed any inflammatory changes. We believe that our observation of the case not only confirms the prevalent opinion that thrombo-angitis obliterans begins in the veins, but also suggests that the inflammatory process stressed by Buerger as the initial process may, in reality, be the terminal process, taking place only after the vessels have become thrombosed and devitalized.

SUMMARY

Venofibrosis (phlebosclerosis) is entirely different from arterio (athero)sclerosis, there being no evidence of fatty changes or of calcification, the entire process is apparently noninflammatory, and the histologic picture presents a varying degree of endothelial or sub-endothelial and medial replacement fibrosis.

The cases seen by us have invariably occurred in men under 40 years of age, none of them showing the slightest tendency to simulate—clinically—arterial lesions, a great majority of the patients had small hearts and low arterial tension, in other words, while venofibrosis may occur with arteriosclerosis, it is independent of it.

Venofibrosis is not rare, but is rarely recognized, because it is rarely looked for. The experience of Martin and Meakins, of Martin and Tull and of Widal and Bezançon testify to that effect. This lesion may indicate what Pende calls constitutional deficiency in the structure of the vascular wall. Most of our cases seem to be associated with peptic ulcers.

It is reasonable to assume that veins because of their weaker structure and greater exposure to injurious elements would be a more common site for lesions than the arteries.

Thrombo-angitis obliterans begins in the veins, and the condition is not inflammatory, the inflammation associated with it is a terminal process occurring after the vessels have become thrombosed and devitalized.

OCCURRENCE OF NUMEROUS LARGE GIANT CELLS IN THE TONSILS AND PHARYNGEAL MUCOSA IN THE PRODROMAL STAGE OF MEASLES

REPORT OF FOUR CASES^{*}

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The four cases of the prodromal stage of measles in which tonsillectomy was done reported in this paper showed extraordinary tonsillar pathologic changes, and as measles developed in all four of the patients within from one to five days after tonsillectomy, these pathologic changes may be reasonably ascribed to the measles. Further, the occurrence of measles was correctly predicted in three of the cases, based on the same changes as were found in the first case, in which typical measles developed two days after the tonsillectomy. Moreover, the pathologic observations on the tonsils in these four cases were the only observations of that type made on about 50 000 tonsils examined in this laboratory to the time of writing, also as far as known the four patients were the only ones in whom measles developed within a few days after tonsillectomy.

REPORT OF CASES

CASE 1—C T a boy, aged 11, had frequent attacks of tonsillitis and sore throat, especially during the winter months. He breathed through his mouth. The clinical diagnosis was septic tonsils and adenoids. Tonsillectomy was performed on Dec 26, 1929. The tonsils were examined pathologically on Dec 27, 1929. They showed marked lymphoid hyperplasia, hyperkeratosis and increase of stroma, they did not show tubercles. The most striking feature was the presence of great numbers of large giant cells in the germinal centers, and particularly beneath the epithelium of the crypts. At first it was thought that the condition was early Hodgkin's disease or malignant lymphoblastoma. A biopsy of one of the cervical glands was immediately carried out, but no giant cells were present in the gland, and no evidence of lymphoblastoma, the gland presenting the picture of simple lymphadenitis. Two days after the tonsillectomy the boy had a temperature of 102.5 F, coryza and mild conjunctivitis, with Koplik's spots on the mucous membrane of both cheeks. Two days later the fully developed eruption of measles was present. The recovery was uneventful.

CASE 2—M M, a boy, aged 4, had frequent attacks of tonsillitis and colds. There was chronic otitis media of the left side. The tonsils were enlarged. Adenoids were present. Tonsillectomy was performed on April 10, 1930. The

^{*} Submitted for publication, Oct 22, 1930.

† Dr Warthin died on May 23, 1931.

tonsils showed marked lymphoid hyperplasia, hyperkeratosis, increase of stroma with colonies of mouth organisms in crypts. No tubercles were found. In addition the tonsils presented the same extraordinary picture of numerous large giant cells in the germinal centers and beneath the epithelium of crypts, as well as in the mucosa between the epithelial cells. On the strength of the experience in case 1 inquiry was made as to the possibility of the child's having measles or having been exposed to measles with negative results. Three days later he presented coryza, conjunctivitis, Koplik's spots and fever. Two days later, he had a fully developed attack of measles.

CASE 3—M. D., a girl, aged 8, had frequent attacks of bronchitis and tonsillitis. She had had otitis media every winter for four years. The clinical diag-

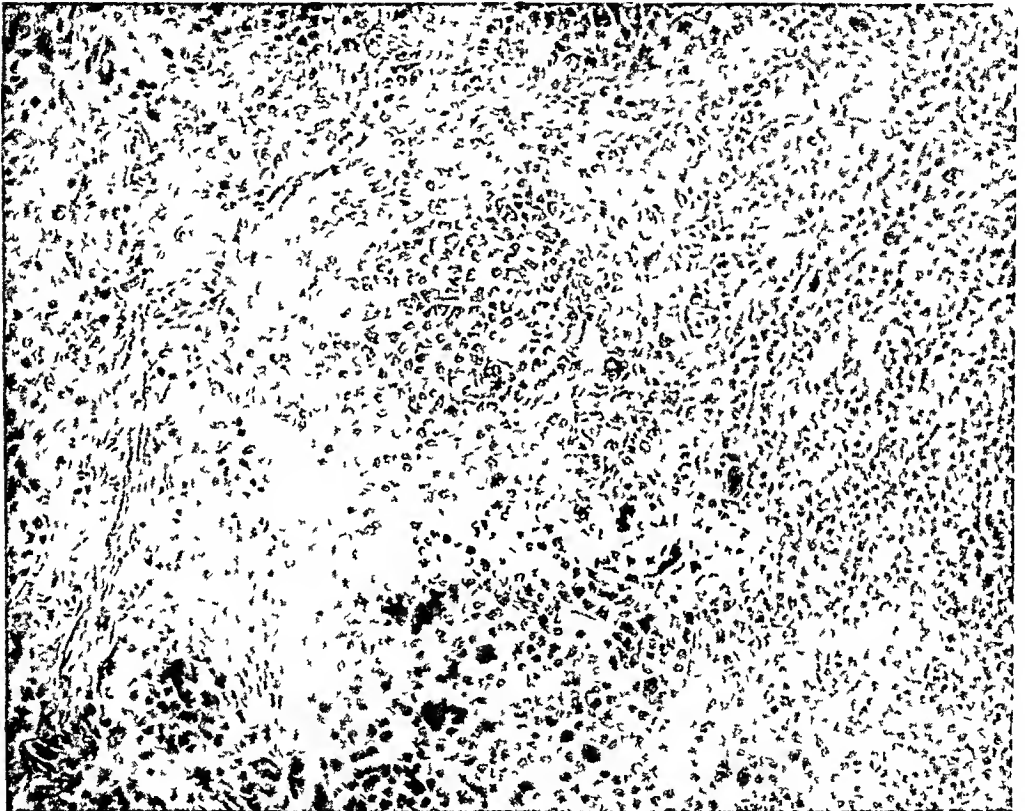


Fig 1—Low power view of the mucosa of a tonsil in case 2, removed five days before a fully developed attack of measles. Multinucleate giant cells are closely crowded in the subepithelial layer.

nosis was septic tonsils and adenoids, with chronic otitis media of the left side. Tonsillectomy was performed on June 13, 1930. The tonsils showed lymphoid hyperplasia, hyperkeratosis, increase of stroma and colonies of mouth organisms in crypts. No tubercles were seen. In addition the tonsils presented the same picture of large giant cells in germinal centers and beneath and in the epithelium of the mucosa as in cases 1 and 2. A prediction of measles was made at once. Thirty-six hours after the operation the child began to have high fever, a blotchy maculopapular eruption and sore throat, with watery eyes. Koplik's spots were not present. After about thirty-six hours duration the rash began to fade slowly and the temperature came down. There was a clinical difference of opinion as to



Fig 2—Higher power view of a portion of the mucosa of a crypt from a tonsil in case 2, showing the multinucleate giant cells beneath the epithelium

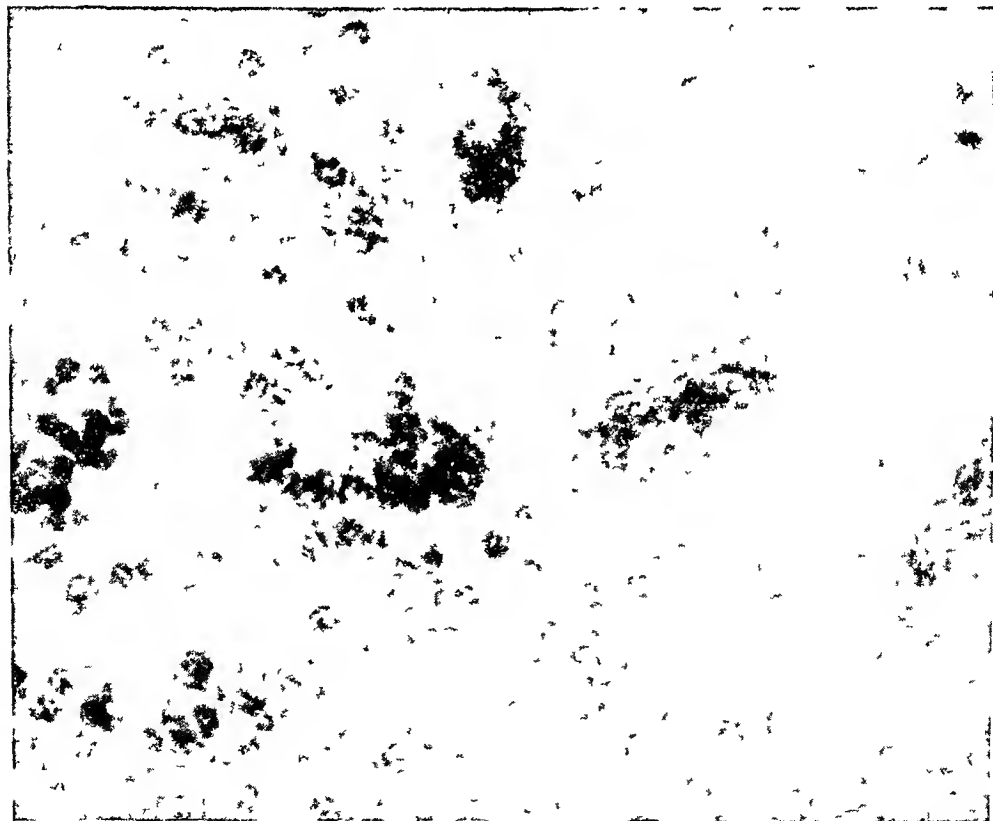


Fig 3—High power view of subepithelial giant cells in case 2. The round, granular nuclei are well shown

whether or not the condition was measles, but this diagnosis was concurred in by the majority of the medical men who examined the patient

CASE 4—Only one other pair of tonsils showing pathologic changes identical with those shown in cases 1, 2 and 3 had occurred in the tonsil material of this laboratory, aggregating about 50,000 cases, to the time of writing In May, 1926, tonsils were received from St Lawrence Hospital, in Lansing, Mich These were from a girl, B C, a patient of Dr A E Owen The pathologic diagnosis returned was "Marked lymphoid hyperplasia with marked exhaustion of germinal centers and many atypical lymphoblasts Giant cells and cells of mveloid type This child must have some severe systemic process Is there a general swelling



Fig 4—Germinal center from a tonsil in case 2 showing the lymphoid exhaustion of the center, the prominence of the lymphoblasts and numerous multi-nucleated giant cells in various stages of formation A superficial resemblance to Hodgkin's disease is suggested

of lymph nodes? Has the child had infectious mononucleosis? What is the blood count? Please give us history " No answer to these inquiries was received After the tonsils in the other three cases had been examined in the laboratory a positive diagnosis of measles was made in this case, and a letter was written to Dr Owen, asking whether his patient had not had measles following the tonsillectomy In his reply of Oct 6 1930 Dr Owen wrote "In reply to your inquiry, beg to advise that this patient did have measles developing the day following operation " This made the third case in which the prediction of measles based on the pathologic observations in the tonsils was confirmed

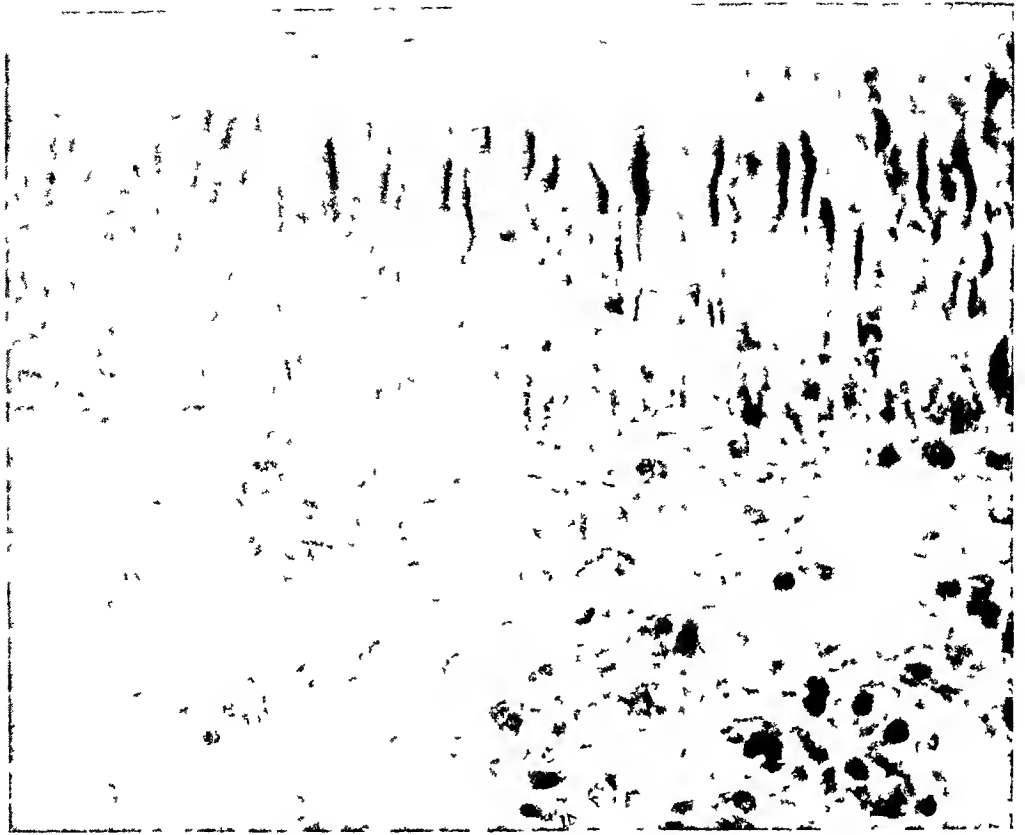


Fig 5—Mucous membrane from the nasopharynx in case 2, showing subepithelial formation and infiltration by multinucleate giant cells

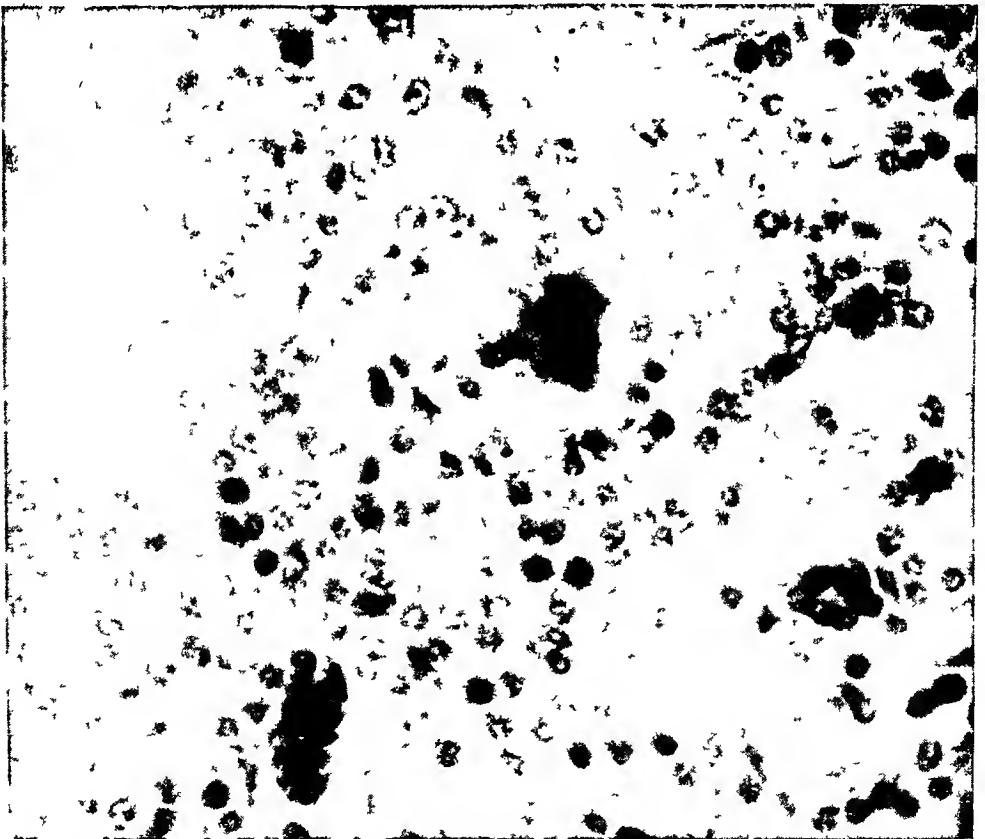


Fig 6—Multinucleate giant cells in subepithelial lymphoid tissue of a tonsil in case 2. Two congested capillaries are shown in part. Note the noninvolvement of the vascular endothelium.

Pathologic Observations in Cases 1 to 4—The tonsils and adenoids in the four cases of the prodromal stage of measles in which tonsillectomy was done all showed the same pathologic features. Beneath the epithelium of the tonsillar surface and crypts, there was a narrow zone filled with large, syncytial, multinucleate giant cells. They were round or irregularly lobed. They showed no peripheral arrangement of the nuclei. No cells of the Langhans type were seen. The nuclei were arranged in a grapelike cluster in the center of the cell. They were granular and stained lightly with hematoxylin. Similar cells were found in the mucosa between the epithelial cells, and also in the germinal centers. There were a few in the lymphoid tissue between the germ centers. The giant cells varied greatly in size and in the number



Fig 7—Low power view of tonsillar mucosa in case 4, showing the numerous subepithelial multinucleate giant cells

of nuclei, although the majority were large, many of them averaging about 100 microns. There were some with as many as from 70 to 100 nuclei. The largest had a rather scanty cytoplasm that stained bright red with eosin. In these large forms the nuclei were often pyknotic and fragmented. One received a definite impression that the giant cells arose by amitotic division in hyperchromatic cells resembling lymphocytes in the subepithelial reticulo-endothelial layer and in the germinal centers, and wandered toward and into the mucosal epithelium. In the latter there were numerous elongated forms between the epithelial cells, with their long axes toward the surface. All possible transition stages of development from the hyperchromatic lymphocyte form to the largest multinucleated giant cells were present. The great majority of these showed nuclei in various stages of harbor-

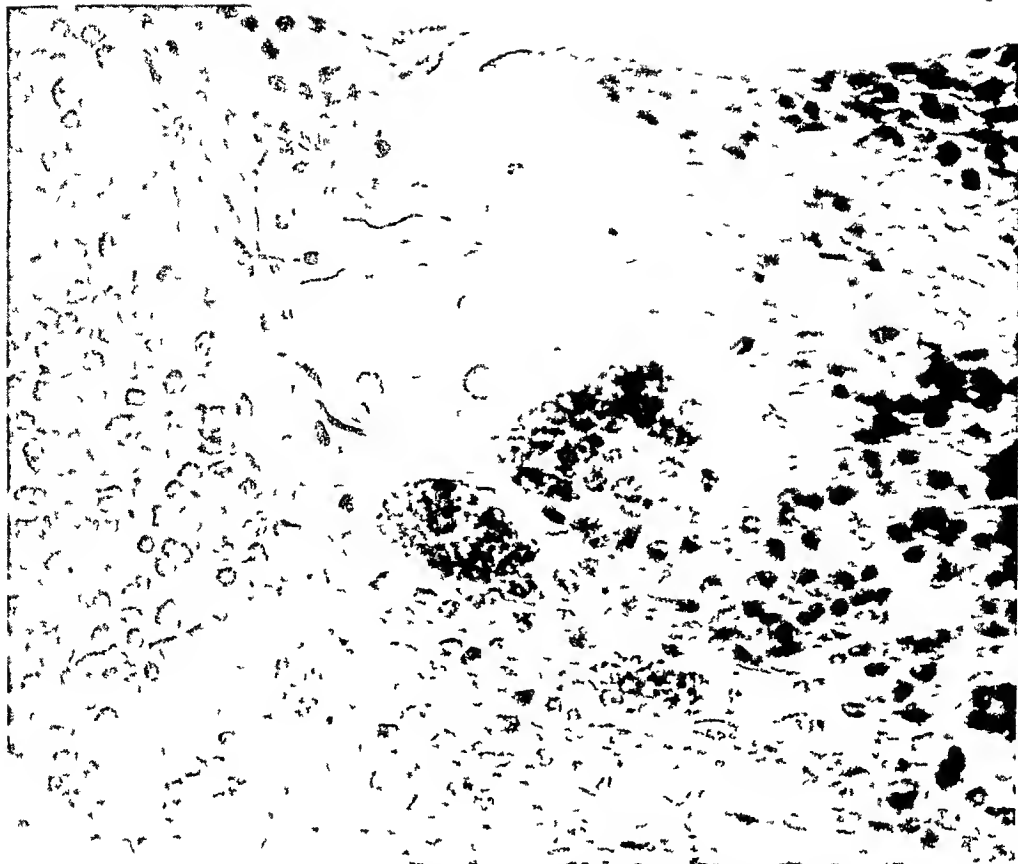


Fig 8—Higher power view of the tissue shown in figure 4, showing the characteristic clustered nuclei of the subepithelial giant cells

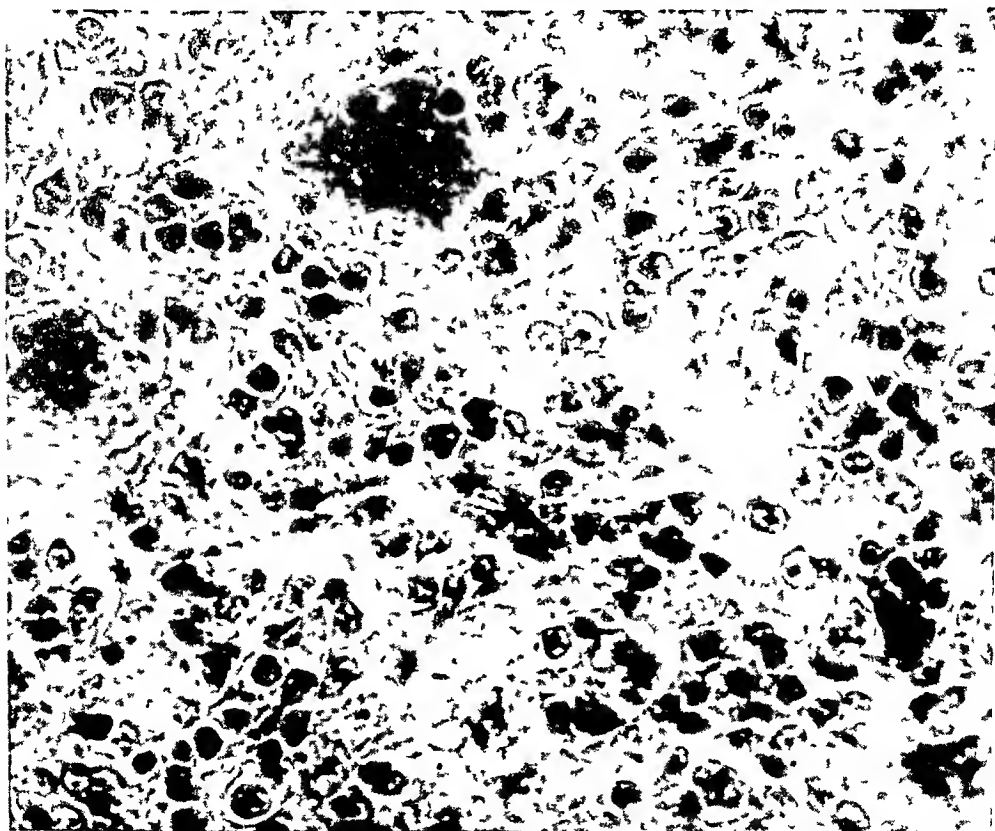


Fig 9—Large multinucleated giant cells in subepithelial lymphoid tissue of tonsils in case 4

thevis and pyknosis. The low power view of these tonsils presented a striking picture, as the epithelium of the surface and of the crypts was outlined by a zone of giant cells. Aside from the giant cells the tonsils presented little change varying from that of the ordinary enlarged tonsil. The germinal centers, particularly those near the epithelial surfaces, showed a marked lymphoid exhaustion with large, pale, swollen, maternal lymphoblasts and giant cells. The blood vessels near the surface were congested, and there was occasionally a minute hemorrhage where the giant cells were aggregated in the largest number. There was no evidence of any of the giant cells arising from the vascular endothelium. No cell inclusions were found in the latter. The pharyngeal mucosa from the adenoids in these four cases showed precisely similar pathologic changes.

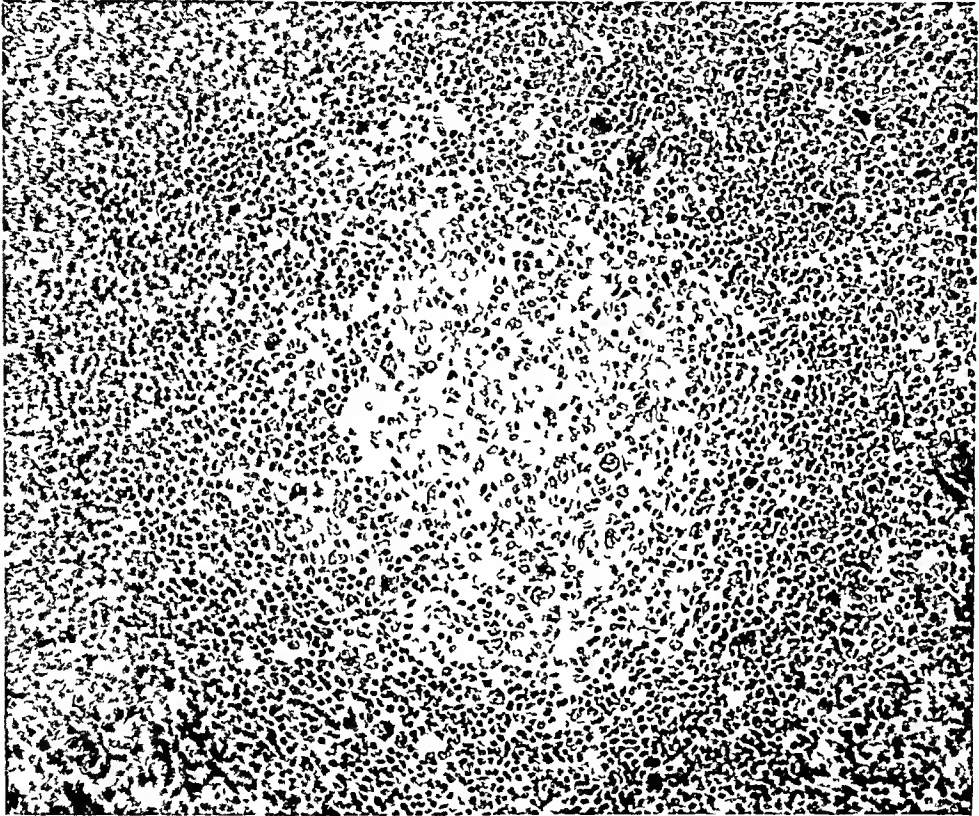


Fig 10—Germinal center from a tonsil in case 4, showing characteristic lymphoid exhaustion, prominence of lymphoblasts and various stages of formation of multinucleate giant cells

COMMENT

The interpretation of these changes can be only that they are defensive. In the giant cells is most probably to be found the etiologic agent of measles. Nevertheless, staining with diverse bacteriologic technical methods failed to reveal any intracellular micro-organisms or inclusions in any way resembling parasites. In all four cases however, the tonsillar tissues contained great numbers of a shortchained streptococcus the individual cocci being slightly oval in form. No spirochetes

or spirilla could be demonstrated by the silver impregnation methods. No evidence of phagocytosis of the streptococci by the giant cells could be obtained.

The tonsils in these four cases present a unique pathology not seen in any other instance in the tonsils of 50,000 patients that have been examined in this laboratory. Nor do the records show that there was any other prodromal case of measles in this material. It, therefore, seems reasonable to connect this pathology with the measles. I feel confident that these changes represent the essential pathology of measles in the upper part of the respiratory tract, and that these giant cells must be phagocytic for the etiologic agent of measles, whatever this may be. I regret the inability to demonstrate this agent. Nearly 50 special staining methods for the demonstration of micro-organisms in tissues have been tried out on sections from these four cases, but without success. This effort will be continued, however, in the hope that something may be found.

Very little has been written on the pathology of the mucous membrane in measles. In 1909 Ewing¹ made a summary of the small number of observations published to that time on the pathologic changes in the skin and mucous membrane in measles, and made some additions. In his conclusion he made the following statement regarding the cell changes in the mucous membrane:

If there is anything specific in these lesions of the mucous membranes it is the extensive subepithelial infiltration with round cells, which often shows a focal distribution, and the focal necroses, and it has seemed to me that the occurrence of the former probably determines the latter lesion in skin, pharynx, and respiratory tract. Koplik's spots seem to be one expression of this focal character of the process. There is a uniformity in the number of large round cells in the derma, and these seem to be divided among exuded large mononuclear leukocytes and multiplying endothelia.

In 1920, Mallory and Medlar² reported a study of the cutaneous lesions in measles. Their material was derived almost wholly from the skin of adult patients showing the fully developed eruption of measles. Buccal mucous membrane containing Koplik's spots was excised from six patients from forty-eight hours before to twenty-four hours after the appearance of the exanthem. These lesions were described as follows:

Microscopically the lesions consist of an exudation of serum and endothelial leucocytes into the stratified epithelium where they usually collect near its outer surface. The epithelial cells in the infiltrated focus undergo necrosis, and the

1 Ewing, James. *J. Infect. Dis.* 6 1, 1909.

2 Mallory, F. B. and Medlar, E. M. *J. M. Research* 41 327, 1920.

leucocytes may collect together so as to form minute pustules. In addition there are retrograde changes in the epithelial cells such as direct division of the nuclei and the formation of granules and globules with basic and acid staining properties. The lesion is exactly like that in the epidermis covering the skin lesions, and corresponds with it in the time of its appearance, but instead of drying up the tissue involved tends to macerate so that slight erosions are formed which may become secondarily infected by organisms present in the mouth, and thus enlarge into shallow or more or less extensive ulcerations.

It will be noted, from the statements quoted that neither Ewing nor Mallory noted the occurrence of multinucleate syncytial giant cells in the lesions of the mucous membrane in measles. Nor do the illustrations by Mallory of the histology of the Koplik spots from the buccal mucous membrane show any indication of their presence. In measles either there is a difference in the pathology of the lesion in the mucous membranes of tonsil and pharynx from that of the buccal mucosa, or these investigators missed what is to my mind the most striking feature of the lesion in the tonsil and pharyngeal mucosa. It seems most probable that they failed to recognize it. Further, no participation of the vascular endothelium in the production of the giant cells was seen in the four cases herein described. The blood vessels were congested, but the endothelium appeared unaltered. No cell inclusions, as described by Mallory, were seen in the endothelium. No focal necroses were observed, but this may have been due to the early nature of these lesions which were prodromal to the exanthem. Certain aggregations of the giant cells, with greater localized congestion and edema, suggested potential Koplik's spots. In the case in which the exanthem appeared on the day after the tonsillectomy a greater number of degenerating giant cells were found in the mucosa between the epithelial cells and even on their surface.

CONCLUSION

The essential pathologic lesion in the tonsils and pharyngeal mucosa in the prodromal stage of measles (from twenty-four to ninety-six hours before the exanthem) is a subepithelial infiltration of multinucleate syncytial giant cells, lymphocytes and monocytes, wandering of the giant cells into the mucosa and on to its surface, with edema and congestion, marked lymphoid exhaustion of the germinal centers with production of the multinucleate giant cells from cells of the lymphoblast type and migration of these cells toward the mucosa. Local aggregations of the giant cells, with more marked local edema and congestion suggest potential Koplik spots. This pathology is so distinctive that a positive diagnosis of measles may be made from one to five days before the exanthem appears. The process is interpreted as a

defensive one directed to an etiologic agent, either in or on the pharyngeal mucosa. This bears out the view of a primary respiratory infection. No evidence of phagocytosis by these giant cells could be obtained by the use of a large number of staining methods applicable to the demonstration of micro-organisms. No participation in the process by the vascular endothelium was noted, nor could any inclusions be found in the latter.

INTRADURAL TERATOID TUMORS OF THE SPINAL CORD

REPORT OF A CASE *

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Bidermal, or teratoid, tumors of the spinal cord are exceedingly rare. I have not been able to find a single case of genuine tridermal or teratomatous new growth of the spinal cord recorded in the literature. In 1888, Gowers and Horsley¹ collected 58 cases of tumors of the spinal cord. In 1895, Starr² found 123 cases reported. No mention of teratoma or of teratoid tumors was made in these two papers. Schlesinger's monograph³ on 400 collected cases included one of intramedullary and one of extradural teratoma. The 70 cases of tumors of the spinal cord collected by Collins⁴ in 1902 and the 141 by Stursberg⁵ in 1908 included none of teratoma. There was 1 case of teratoma in Flatau's⁶ series of 213. Frazier and Allen⁷ and Steinke⁸ found 1 case of extradural, extramedullary teratoma among the 330 in which operation was performed. Lennep⁹ discussed the 153 cases of spinal tumors in which operation was performed which he found in the literature from 1908 to 1920. No teratoma was mentioned. In Clymer, Mixer and Mella's experience¹⁰ with 52 cases of tumors of the spinal cord during an interval of ten years, a teratoma was not found. Among

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* From the Department of Pathology, Albany Medical College, and the Pathological Laboratory of the Albany Hospital

1 Gowers, W. R., and Horsley, V. *Tr. Med.-Chir. Soc.* **71** 377, 1888

2 Starr, M. A. *Am. J. M. Sc.* **109** 613, 1895

3 Schlesinger, H. *Beiträge zur Klinik der Rückenmarks- und Wirbeltumoren*, Jena, Gustav Fischer, 1898

4 Collins, J. *M. Rec.* **62** 882, 1902

5 Stursberg, H. *Centralbl. f. d. Grenzgeb. d. Med. u. Chir.* **11** 91, 141, 185, 225 and 277, 1908

6 Flatau, E., in Lewandowsky, M. *Handbuch der Neurologie*, ed. 7, Berlin, S. Karger 1911, vol. 2 p. 616

7 Frazier, C. H., and Allen, A. R. *Surgery of the Spine and Spinal Cord*, New York, D. Appleton & Company, 1918, chap. 8 p. 498

8 Steinke, C. R. *J. Nerv. & Ment. Dis.* **47** 418, 1918

9 von Lennep, H. *Deutsche Ztschr. f. Chir.* **160** 136, 1930

10 Clymer, G., Mixer, W. J., and Mella, H. *Proc. Boston Soc. Psychiat. & Neurol.*, Nov. 18, 1920, *J. Nerv. & Ment. Dis.* **53** 229, 1921

the 100 verified tumors of the spinal cord reported by Elsberg,¹¹ no teratoma was listed. Elsberg and Constable¹² recently analyzed 45 cases of lesions of the cauda equina, which did not include a teratoma. Those complex tumors of the spinal cord listed as teratomas in the literature have turned out to be teratoid, or bidermal, on personal study of the microscopic descriptions of the recorded cases.

The case of teratoid tumor of the spinal cord here presented occurred in the medical service of Dr. Thomas Ordway and the neurosurgical service of Dr. Arthur H. Stein of the Albany Hospital, both of whom provided me with the details of the clinical history of the patient.

REPORT OF CASE

History—R. S., 24 years old, married, a toolmaker, was seen by Dr. Thomas Ordway in consultation with Dr. Charles K. Burt, in Lake George, N. Y., on Aug. 18, 1922. As a child, he had whooping cough and measles. There was a vague history that for a short time he could not walk, although previously he had been able to do so. The exact nature of this difficulty was never known, but when he tried to enter the army in 1917, it was said that the old trouble was probably the result of infantile paralysis. His family history was not important.

He had been working in the "tests" at the General Electric Company at Schenectady until two weeks before, when he felt a pain in the back in the lumbar region. This was believed to be "rheumatism," for which he was treated during the next few days.

During the week before admission, he had gradually become worse and the pain in the back more intense. A slight, inconstant insecurity of the legs developed. He continued to work until six days before admission, when pains in the legs developed. He went to a mechanotherapist, who applied electricity. Gradually, both lower extremities became so much weaker that he was unable to drive his car.

During the last twenty-four hours, the patient had been in bed and could hardly move his legs. The pain in the back continued. Early in the morning he was unable to pass urine and had to be catheterized. The bowels did not move, and the patient could not even expel the water given by enema. He had repeated spells of vomiting. The pain in the back became severe and was only slightly relieved by hypodermic injections of morphine.

Physical Examination—Physical examination disclosed a well developed, well nourished young man lying in the dorsal decubitus, rather nervous and worried. The skin was somewhat dry. There was a pilonidal cyst in the sacral region. His pupils were equal and reacted normally. There was no demonstrable defect of the cranial nerves. A slight rigidity of the neck was present. The temperature was 101, and the pulse rate 80. There was no gross disorder of sensation, although there was some retardation of localization in the legs and the lower part of the trunk. There were numbness and paresthesias of the legs and intense pain in the back. The umbilical and cremasteric reflexes were present. The knee jerks were markedly exaggerated. The patellar twitch was elicited. There was a slight

11 Elsberg, C. A. *Tumors of the Spinal Cord*, New York, Paul B. Hoeber, 1925. *Diagnosis and Treatment of Surgical Diseases of the Spinal Cord and Its Membranes*, Philadelphia, W. B. Saunders Company, 1916.

12 Elsberg, C. A. and Constable, K. *Arch. Neurol. & Psychiat.* 23:79, 1930.

suggestion of a Babinski sign on the left. There was a bilateral positive Kernig sign. The back was rigid. The muscles were stiff and firm. There had been no convulsions or twitchings. The condition suggested myelitis of the lumbar cord.

Roentgen Examination—The patient was moved to the Albany Hospital, Albany, N. Y., on Aug. 19, 1922, for roentgen examination of the spine. The roentgenograms showed a failure of union of the neural arch of the fifth lumbar vertebra and the first sacral segment suggesting spina bifida occulta. The spine was angulated at the twelfth dorsal vertebra, and the right psoas muscle appeared to be in a state of contraction.

Laboratory Examination—The spinal fluid showed intense xanthochromia. The Pandy test for globulin gave a markedly positive reaction. The cell count

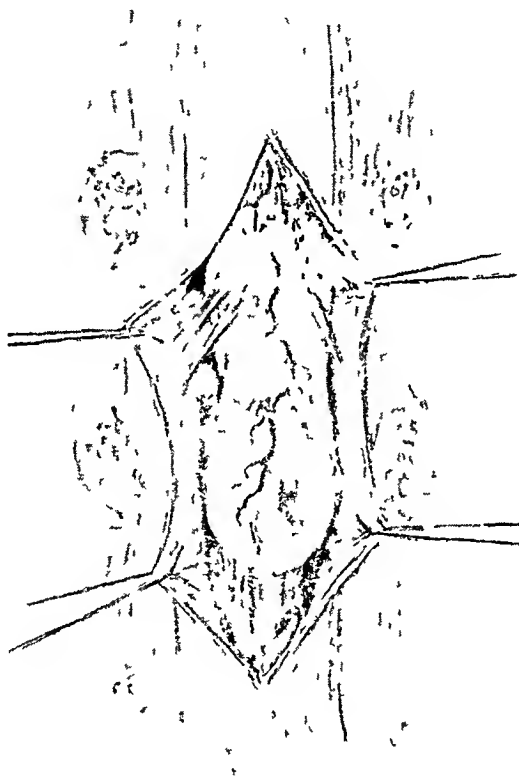


Fig. 1—A drawing of an intradural teratoid tumor of the spinal cord. The dura is reflected to show the general character of the tumor, which was an intimate connection with the posterior aspect of the spinal cord. Note the congested blood vessels coursing over the tumor. The tumor is shown in its natural size. The drawing was loaned by Drs. Thomas Ordway and Arthur H. Stein.

was 2 cells per cubic millimeter. The Wassermann tests on the spinal fluid and blood gave negative results.

Course—There was disturbed sensitivity to heat, cold and pin prick on the soles of the feet, extending in a diminishing degree up the left leg. The patient had almost complete paralysis of the legs, particularly of the left. After a few days, he was able to move the right leg again fairly well, but could flex and

abduct the left only slightly. He could also expel the enema fluid, so that it did not have to be siphoned off. The retention of urine continued, however. In spite of great care in catheterization, cystitis developed.

Operation was performed by Dr. Arthur H. Stein on Sept. 16, 1922, and an intradural tumor of the spinal cord was found at the level of the second and third lumbar vertebrae (fig. 1). On the right, it was intimately connected with the cord itself. On the left, it was somewhat separated from, but pressed deeply on, the cord. A small specimen from this left side was taken for microscopic examination. Evidence of a considerable amount of old hemorrhage was found within the spinal canal. As the tumor could not all be removed, a decompression of the growth at the level of the first, second and third lumbar vertebrae was done.



Fig. 2—A photomicrograph showing the general distribution of the glandular elements among the smooth muscle bundles. The pacinian corpuscles are indicated by arrows. A few fat cells are present. Hematoxylin and eosin, $\times 30$.

to relieve pressure. It was hoped that the tumor might be extruded, and that this might result in improvement in the function of the cord.

There was considerable shock following the operation. The pulse rose to around 135 and was weak and irregular. The color was poor, and there was an elevation of temperature to 101 F. for a few days.

By Oct. 26, 1922, the patient was gradually gaining strength. The annoying, persistent pain, which had so disturbed his sleep, had disappeared. After some time in a wheel chair, he was able to take a few steps. The function of the bladder improved, although there was not yet complete control of the bladder and rectum.

On November 13, the patient was up for a short time. At this time, it was thought that it was better for him to go about with a couple of chairs rather than on crutches, as he was very insecure on his feet.

On November 23, a letter from his physician stated that the patient was able to walk well with crutches. He was rapidly improving, but still had incontinence of urine.

He was gradually able to get about without crutches. His general condition was satisfactory.

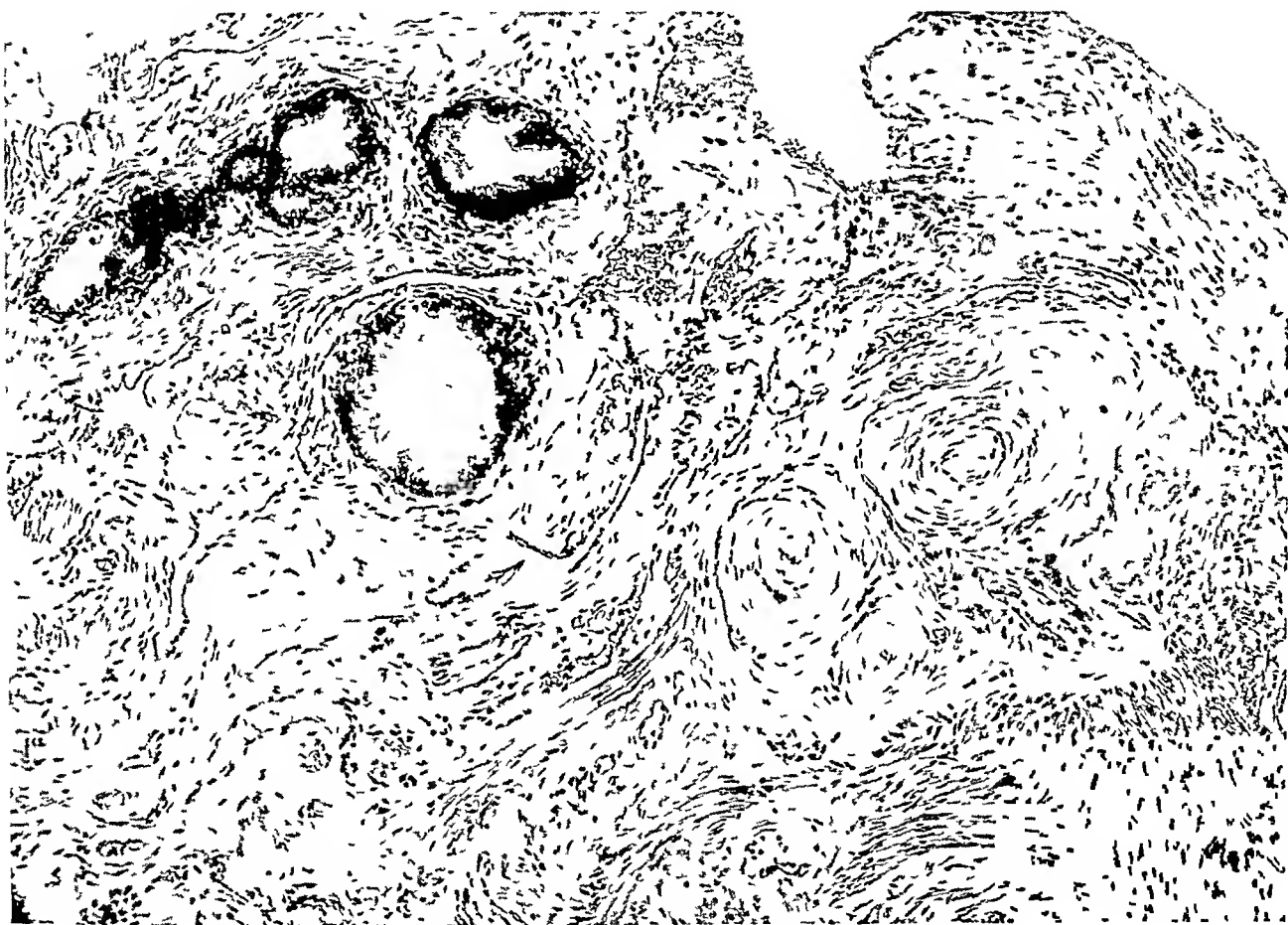


Fig 3—A photomicrograph showing the well formed pacinian corpuscles. The tall columnar cells lining the glands form finger-like projections into the lumen. Many smooth muscle fibers are present in the right half of the section. Numerous thin-walled vascular channels are seen. Hematoxylin and eosin, $\times 119$.

On July 22, 1930, the patient wrote a letter to Dr Ordway, stating that he was still with the General Electric Company, was feeling well, and could drive his car again. However, as some dribbling of urine continued, he had to wear a urinal all the time. He was annoyed most by the constant drainage from trophic ulcers on his feet.

Microscopic Examination of Tumor—Block serial sections, cut from the entire specimen that was removed for biopsy, were stained with hematoxylin and eosin,

Mallory's eosin and methylene blue, aniline blue, phosphotungstic acid and hematoxylin, Perl's prussian blue iron method and the silver impregnation method of Hasegawa¹³

A rather compact, but apparently purposeless arrangement of bundles of smooth muscle fibers made up the bulk of the various sections. The muscle bundles were separated by thin strands of dense collagen. A few fat cells were present here and there. A number of pacinian corpuscles and nerve trunks were embedded between the muscle fibers. These tactile corpuscles were well formed (fig 2).

Glands occurring singly and in small groups, were distributed throughout the sections. All of these glandular structures were lined with both ciliated and non-ciliated epithelia, supported by a single layer of flat basement cells. The large spheroid or ovoid nucleus was generally located nearer the inner border of the cell. The lumina of the smaller glands appeared round or oval, and were lined by cuboidal cells. The larger glands were irregular in shape. The lining epithelium here varied from cuboidal to tall columnar and formed finger-like projections into the lumen. A closer study of the lining cells under high power showed that the free borders of the individual cells were not uniformly even. The free border of some of the cells extended farther out into the lumen, like little pseudopods. Most of the lining cells contained varying amounts of finely granular, yellowish pigment in their cytoplasm. This pigment did not give a positive prussian blue reaction for iron. However, that iron was present in some of these cells was evidenced by the presence of fine, blue, dustlike particles. These yellowish granules did not reduce an ammoniacal solution of silver after the method of Hasegawa, in other words, the pigment granules were not argentaffine. In sections stained with phosphotungstic acid and hematoxylin, none of these cells contained blepharoplasten along the free borders, so that the glandular structures were probably not of endodermal origin. Some of the structures suggested sweat glands or the glandular tissue of the breast or of the prostate (fig 3).

COMMENT

In a previous paper,¹⁴ teratomas and teratoid tumors of the brain were discussed. Compared with the hundreds of other tumors of the brain and of the spinal cord reported, those developing from multipotential or totipotent cells are rare. Many of the structures found in these complex tumors are often difficult to classify, owing to the frequently undifferentiated or abortive character of the derivatives of the three primitive germ layers. Frequently, too, the ectodermal and mesodermal elements tend to overgrow at the expense of the endodermal elements, which may either become retarded in their growth or disappear entirely. For this reason, it may be extremely difficult to judge whether a tumor under consideration is of multipotential origin (teratoid) or of totipotent origin (teratomatous).

These teratoid tumors are obviously congenital. They are often associated with other congenital abnormalities or defects. One of the

13 Hasegawa, T. Virchows Arch f path Anat **244-245** 8, 1923

14 Hosoi K. Arch Path **9** 1207, 1930

cases of Kubie and Fulton¹⁵ and the case here reported showed spina bifida occulta and a pilonidal cyst. Hansmann's¹⁶ case was a veritable pot-pourri of congenital defects. There was an associated syringomyelia in the cases of Gerlach,¹⁷ Andre-Thomas and Quercy¹⁸ and Bielschowsky and Unger¹⁹.

It may not be amiss to mention here the few recorded cases of extradural, intravertebral teratoid or teratomatous tumors. Virchow²⁰ described an extradural, intravertebral tumor composed of fibrous connective tissue, fat and cartilage. In Brun's²¹ case, an extradural growth surrounded the cord for a considerable distance in the form of a cylindric jacket. In their review of 330 collected cases of spinal tumors in which operation was performed, Frazier and Allen⁷ mentioned an extradural, extramedullary tumor in the lumbosacral region in a man between 30 and 39 years of age.

The table shows that three of the ten cases occurred in childhood.

Since these complex tumors are benign and grow slowly over a period of many years, the acute symptoms of pressure on the spinal cord may not arise until in adult life. In the case here reported, it is to be noted that this young man gave a vague history of not being able to walk for a short time when a child, although previously he had been able to do so. The clinical aspects of spinal tumors have already been discussed exhaustively in the various excellent monographs referred to.

As regards sex, the tumors occurred in five males and three females. Though this series of cases of tumors of the spinal cord is too small to be of any significance, it is interesting to note that similarly both the teratomatous and the teratoid tumors of the brain more frequently affected the male sex.

Histologically, only the derivatives of the mesodermal elements were present in the cases of Gowers,²² Gerlach¹⁷ and Forbes.²³ Frick²⁴

15 Kubie L. S., and Fulton J. F. *Surg Gynec Obst* **47** 297, 1928.

16 Hansmann, G. H. *Surg Gynec Obst* **42** 124, 1926.

17 Gerlach W. *Deutsche Ztschr f Nervenhe* **5** 271, 1894.

18 Andre-Thomas and Quercy. *Nouvelle icon de la Salpêtrière* **25** 364 1912.

19 Bielschowsky M., and Unger, E. *J f Psychol u Neurol* **25** 173, 1920.

20 Virchow R. *Die krankhaften Geschwulste*, Berlin, A. Hirschwald, 1863, vol 1, p 514.

21 Bruns, L. *Rückenmarkstumoren*, in Eulenberg, A. *Encyclopadische Jahrbucher der gesamten Heilkunde*, Fünfter Jahrgang, Leipzig, Urban & Schwarzenberg 1895, p 533, *Die Geschwulste des Nervensystems*, Eine klinische Studie Berlin, S. Karger, 1897, p 274.

22 Gowers, W. R. *Tr Path Soc London* **27** 19, 1876.

23 Forbes, J. G. *St Barth Hosp Rep* **41** 221, 1905.

24 Frick K. *Frankfurt Ztschr f Path* **7** 127, 1911.

Reported Cases of Teratoid Tumors of the Spinal Cord

No	Author	Sex	Age, Years	Location	Size	Teratodermal Structures	Mesodermal Structures	Structures Hard to Classify
1	Gowers, 1876		Adult	Conus medullaris	0.5 by 0.5 by 0.4 in		Connective tissue, striated muscle, fat	
2	Gerlach, 1894	M	36	Upper cervical	About 3 mm long		Connective tissue, primitive and adult muscle fibers, cartilage	Embryonal tissue
3	Orbés, 1905	M	5.5	Midcervical	Size of haricot bean		Cellular connective tissue, embryonal and adult striated muscles, fat cells, multinucleated giant cells (osteoclasts?)	
4	Friel, 1911	F	41	2d to 5th lumbar vertebrae		Numerous blond hairs	Connective tissue, bone with myeloid tissue in marrow, fat	
5	André Thomas and Querey, 1912			Cervical and dorsal cord		Pendymal cells, glial elements (glioma)	Connective tissue, striated muscle, numerous blood vessels	
6	Bielschowsky and Unger, 1920	M	17	3d cervical segment	Twice walnut size	Fine hairs	Connective tissue, fat cells, endothelium or alveolar sarcoma	
7	Hansmann, 1926	F	21 days	Sacral	6 cm diameter	Stratified squamous epithelium, nerves, glial cells, ependyma, ependymal glioma (?)	Myomatous connective tissue, smooth muscle, cartilage, fat, lymphoid cells	Cysts lined with high columnar cells
8	Kubie and Fulton, 1928	M	2	9th dorsal to 1st lumbar	6 by 1.5 cm	Mucous and serous glands, large myelinated nerve fibers	Connective tissue, smooth muscle	Cysts lined with ciliated columnar cells
9	Kubie and Fulton, 1928	F	27	3d and 4th cervical		Mucous and serous glands, myelinated nerve fibers, ganglion cells (?)	Connective tissue, smooth muscle, fat, cartilage, lymphoid tissue	Cysts lined with ciliated euboidal to columnar cells
10	Hosoi, 1930	M	24	2d and 3d lumbar	About 1.5 by 3.5 cm	Nerve fibers, paelman corpuscles	Connective tissue, smooth muscle, fat cells	Glands lined with ciliated and non ciliated columnar cells

described a teratoid tumor containing bone with myeloid reaction in the marrow spaces. It is difficult to say just what is the nature of the cysts or glands lined by ciliated and nonciliated, tall columnar cells. In two of the reported cases there were an associated glioma and an endothelioma or alveolar sarcoma. Endodermal elements were uniformly lacking, so that all of the collected complex tumors of the spinal cord are bidermal. Intradural tridermal tumors or genuine teratomas are perhaps yet to be described.

SUMMARY

Complex tumors of the spinal cord are of extreme rarity. Nine cases are recorded among the hundreds of reported tumors of the spinal cord. An additional case of teratoid tumor of the lumbar spinal cord in a young man, who had spina bifida occulta and a pilonidal cyst, is here reported. Owing to early spinal decompression, he regained the use of both of his lower extremities. Only a slight incontinence of urine was left.

RUPTURED ANEURYSM OF THE CYSTIC ARTERY OF THE GALLBLADDER AS A RESULT OF TOXIC ARTERITIS

REPORT OF A CASE¹

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Judged from the literature, aneurysm of the cystic artery is rare. Four cases have thus far been reported. Its interest, however, lies, not in its rarity, but rather in the mechanism of its formation.

In 1883 Chiari¹ reported a case of multiple (two) aneurysms of the cystic artery associated with ulcerative cholecystitis and cholelithiasis. One of the aneurysms had ruptured as a result of the irritation of a passing stone. On microscopic examination, he found that the media and the adventitia of the vessel had been eroded by an ulcer, and that the intima had herniated through to form a true aneurysm.

In 1917, Klotz² described a case of multiple aneurysms of the cystic and hepatic arteries. The underlying cause was a generalized periarteritis nodosa. Microscopically, he found a perivascular accumulation of lymphocytes and leukocytes, with an accompanying hyaline degeneration of the media. The intima and the outer coats were secondarily involved by the inflammatory process. The same author described a second case similar to the first, except that the aneurysmal involvement was limited to the hepatic artery.

In 1920, Hogler³ reported a case of aneurysm of the cystic artery in which rupture had occurred into the cystic duct. Microscopically, atherosclerotic changes were present in the vessel. The aorta and the celiac artery were similarly involved.

Walter's⁴ case of periarteritis nodosa, described in 1921, was similar to that of Klotz.

Aneurysms of the hepatic artery are more common. In 1923, Friedenwald and Tannenbaum⁵ gathered 65 cases (including one

¹ Submitted for publication, Oct. 14, 1930.

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1 Chiari, H. Berstung eines Aneurysmas der Arteria cystica in die Gallenblase mit tödlicher Blutung. *Prag med Wchnschr* 8:33, 1883.

2 Klotz, O. Periarteritis Nodosa. *J M Research* 37:1, 1917.

3 Hogler, F. Beitrag zur Klinik des Leber und Milzarterien Aneurysmas, *Wien Arch f inn Med* 1:509, 1920.

4 Walter, H. Periarteritis nodosa. *Frankfurt Ztschr f Path* 25:306, 1921.

5 Friedenwald, J., and Tannenbaum, K. H. Aneurysm of the Hepatic Artery, *Am J M Sc* 165:12, 1923.

case of their own) of aneurysms of the hepatic artery and its branches. In 50 instances, the causative factors were known and were, with the number of cases, as follows: general infections, 7, typhoid fever, 2, pneumonia, 5, empyema, 1, osteomyelitis, 3, arteriosclerosis, 12, cholelithiasis, 5, syphilis, 7, and trauma, 8. They did not mention periarteritis nodosa as a factor as in the cases of Klotz and Walter.

Additional cases of aneurysm of the hepatic artery have been reported by Thompson⁶ (erosion of the vessel by a tuberculous gland), Muller⁷ and Aschner⁸ (atherosclerosis) and Stokes⁹ (suspected mycotic aneurysm in a case of malignant endocarditis, see also Eichelter and Knoflach¹⁰).

The case reported in this paper is that of an aneurysm of the cystic artery, found in association with an ulcerative cholecystitis and cholelithiasis. Because the entire cystic artery was the seat of an inflammatory and toxic process, various stages in the development of the aneurysm could be studied. Its pathogenesis differed from that of any of the aforementioned cases.

For this study, serial sections were made of the cystic artery. Hemalum and eosin, van Gieson and elastica stains were made on alternate sections.

REPORT OF CASE

History.—A white man, aged 58, a machinist, was a habitual drunkard, and had entered the hospital on several occasions after an alcoholic debauch. His history was therefore unreliable. In April 1928, he entered the hospital with impending delirium tremens. On physical examination he was found to be icteric. The heart and lungs were essentially normal. The abdomen was protuberant, and the skin contained many striae albicantes. The liver was 8 cm. below the right costal margin and had a sharp edge. The spleen was also palpable and extended to the crest of the ileum. The rectal examination revealed hemorrhoidal tags. There was a slight edema of the lower extremities. The diagnosis made at the time was that of alcoholic cirrhosis. He remained in the hospital for six days, his jaundice clearing rapidly, and at no time did he complain of abdominal pain.

In October, 1929 (one and one-half years later), he returned to the hospital complaining of a tired feeling and of weakness and cramps in his muscles and legs. He also complained of "spells" characterized by marked weakness and throbbing temporal headache associated with tinnitus and a tendency to see double. On being questioned, he denied having any abdominal distress.

⁶ Thompson, W. P. Tuberculous Aneurysm of the Hepatic Artery, *Bull. Johns Hopkins Hosp.* **42**: 113, 1928.

⁷ Muller, H. R. Aneurysm of the Hepatic and Gastroduodenal Arteries with Rupture into the Duodenum, *Proc. New York Path. Soc.* **20**: 46, 1920.

⁸ Aschner, P. W. Aneurysm of the Hepatic Artery, *Internat. Clin.* **2**: 334, 1923.

⁹ Stokes, E. H. Aneurysm of Hepatic Artery Associated with Acute Endocarditis, *M. J. Australia* **2**: 346, 1926.

¹⁰ Eichelter, G., and Knoflach, J. G. Rupturiertes mykotisches Aneurysma der Arteria gastropiploica dextra, *Deutsches Arch. f. Chir.* **198**: 416, 1926.

He had had in the past, influenza, erysipelas and gonorrhea. He said that he had never had a chancre.

Physical Examination—On physical examination, he was slightly icteric, but not acutely ill. His temperature was normal, the pulse rate was 78, and the respiratory rate, 24 per minute. The blood pressure was 140 systolic and 80 diastolic. The heart and lungs were essentially normal. The liver was 7 cm below the right, and the spleen, 6 cm below the left, costal margin. There was no tenderness over the abdomen. The extremities were slightly edematous.

The urine was positive for bile, but was otherwise normal. The stools were light gray and contained no bile.

The results of examination of the blood were hemoglobin, 75 per cent, red blood corpuscles 3,920,000, white blood corpuscles, 4,850 per cubic millimeter, with 84 per cent polymorphonuclear leukocytes, 12 per cent lymphocytes and 4 per cent eosinophils. The Kahn reaction was negative, and chemical examination of the blood showed that it was normal.

In view of the anemia and the enlarged liver and spleen, the diagnosis was Banti's disease with cirrhosis of the liver.

Course—The patient was fairly comfortable until twenty-five days after his admission to the hospital. Then chills and fever suddenly developed (temperature of 103.4 F, taken rectally), and the patient complained of cramplike pains in the abdomen. These symptoms lasted for only a few hours, but the temperature remained slightly elevated for four days, varying from 99 to 100 F.

The stools at the time of the attack and until the time of death were tarry.

After remaining free from fever for six days, the patient again suffered a chill and complained of severe abdominal pain which was relieved only by a hypodermic injection of morphine sulphate. Five hours later, the pain returned, this time he vomited a large amount of dark, liquid blood and undigested food. His pulse became rapid (120 per minute) and weak, his respirations were labored (36 per minute), and his temperature was subnormal (96.4 F, taken rectally). Eight hours later, he became stuporous. Death occurred twelve hours after the onset of the acute symptoms.

Diagnosis—The final diagnosis was Banti's disease with cirrhosis of the liver, acute cholecystitis and cholelithiasis and rupture of an esophageal varix.

Postmortem Examination (Dr R. H. Jaffe)—The body weighed 175 pounds (79.4 Kg) and measured 170 cm in length.

Externally, the skin was of a dirty yellow color, the sclerae were yellow. The mucous membranes were pale. The abdomen was below the level of the chest, but there were striae on the abdomen. The ankles were edematous.

The midline fat of the abdomen was 2 cm thick. There was about 300 cc of a dark red fluid in the abdominal cavity. The edge of the liver was at the umbilical process and at the eighth rib in the right midclavicular line. The transverse colon was firmly adherent to the inferior aspect of the liver. The intestinal loops were moderately distended and covered by thin, blood-tinged fluid. The spleen extended 10 cm below the left costal arch in the midaxillary line.

The heart weighed 465 Gm. The epicardium was studded with red areas ranging in size from that of a pinpoint to that of a pinhead. The myocardium varied in color from yellowish gray to brown and was very friable.

The gallbladder was distended, measuring 9 by 4.5 by 4 cm. The wall was thickened to a breadth of 6 mm, and was firm and grayish white, and embedded in the liver substance. The cavity was filled by soft, semiliquid, purplish-red masses and many dark-brown concretions, which were from 3 to 5 mm in diame-

ter The internal lining of the gallbladder was yellowish white, with irregular defects from 5 to 15 mm in diameter. These defects had shaggy, overhanging edges and a dark-purplish-gray floor. In the middle of the upper wall was a pea-sized sac that bulged into the cavity and contained an irregular rent, 6 by 5 mm. The sac communicated with a medium-sized artery. In the upper and posterior portion of the wall of the gallbladder was a deep ulcerated area, which surrounded an opening 2 mm in diameter, that led into the abdominal cavity. The abdominal opening was posterior to the transverse colon. The extrahepatic bile ducts were patent and contained several mulberry-shaped concretions, from

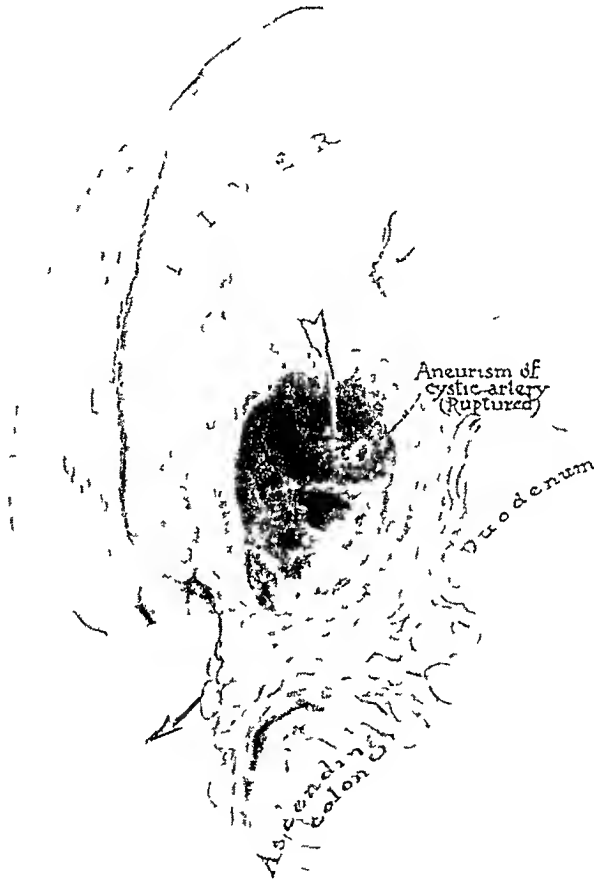


Fig 1—Chronic ulcerative cholecystitis, with rupture of an ulcer into the abdominal cavity as designated by the arrow. The wall of the gallbladder is markedly thickened and is embedded in the liver. The duodenum and ascending colon are adherent to the wall of the gallbladder by dense fibrous tissue. The ruptured aneurysm is seen within the gallbladder (about one-third natural size).

3 to 5 mm in diameter, which were most numerous in the common duct, 2 cm above the papilla of Vater.

The liver measured 32 cm transversely, 20 cm vertically and 10 cm antero-posteriorly. The surface of the liver was studded with granulations, from 1 to 2 mm in diameter, which were light yellowish gray and separated by grayish-white lines. The liver was firm in consistency. The cut surface presented granulations like those described.

The esophageal and the superior hemorrhoidal veins were distended and tortuous

The spleen weighed 2,045 Gm. The surface was smooth and purplish gray, with whitish septal lines. The consistency was soft. The cut surface was purplish red and moderately moist with distinct whitish, slightly elevated follicles, from 1 to 3 mm. in diameter.

The remaining organs presented no significant changes.

Anatomic Diagnosis—The anatomic diagnosis was ruptured aneurysm of the cystic artery, with intracystic hemorrhage, chronic ulcerative cholecystitis, with perforation into the abdominal cavity, intra-abdominal hemorrhage, cholelithiasis and multiple stones in the extrahepatic bile ducts, atrophic cirrhosis of the liver, enormous subacute and chronic tumor of the spleen, dilation of the esophageal and upper hemorrhoidal veins, eccentric hypertrophy of the heart and fatty degeneration of the myocardium, severe cloudy swelling of the kidneys, tarry intestinal content, and chronic icterus.

Microscopic Examination—In the liver, small islands of cells were separated by much fibrous tissue, which was loosely infiltrated by lymphocytes and contained cords of atrophic liver cells and proliferated bile ducts. The liver cells of the islands contained granules of lipoid and of greenish-brown pigment. In the connective tissue septums there were many cells filled with fat and iron pigment.

In the spleen, the reticulum was thickened, and the sinuses, which were wide and filled with blood, stood out distinctly. The pulp contained lymphoid cells, plasma cells and a moderate number of granulocytes. The follicles were small and had no germinal centers, their reticulum was not thickened.

In the gallbladder, the epithelium lining the mucosa was entirely absent. The mucosa was markedly thickened by dense accumulations of plasma cells, lymphocytes, leukocytes and fibroblasts. Newly formed connective tissue and capillaries were abundant. In places, ulcers were noted that at times extended to the muscularis. At one point near the aneurysmal sac, such an ulcerated area extended through the muscularis, to meet a similarly ulcerated area in the serosa, forming a complete rent in the wall of the gallbladder, which was filled with blood. The muscularis was hypertrophic, except in the vicinity of the aneurysm, where the muscle fibers were atrophic, and disappeared entirely at the site of the tear. Extensive hemorrhages, as well as inflammatory cells, were scattered throughout the muscularis and mucosa.

In the main branch of the cystic artery, 2 cm. proximal to the aneurysm, the adventitia was markedly thickened by fibrous tissue. The media was wider than normal as a result of hypertrophy of the muscle fibers and an increase in elastic fibrils. The internal elastic membrane was split. The intima was thickened by an increase of elastic fibrils and connective tissue. The endothelium lining the intima was intact.

From a point 1 cm. proximal to the site of the aneurysm, the artery divided into several branches. These were all affected by one or two processes, degenerative or degenerative and inflammatory.

One of the branches of the vessel was bordered on one side by an accumulation of lymphocytes, leukocytes, plasma cells and histiocytes. The connective tissue in this area was loosened. At this point, the adventitia was markedly thickened by a dense meshwork of fine elastic and connective tissue fibrils. The corresponding media was rarefied and thin, and the nuclei of the muscle fibers were pyknotic or absent. The remaining media was hypertrophied and edematous. The internal elastic membrane was split and presented an increase of elastic fibrils on the

intimal side, so that this portion of the intima was thickened. There were no inflammatory cells in the wall proper.

Continuing distally, the adventitia and media of this branch of the artery were invaded by leukocytes and lymphocytes. The media had a break in its continuity which included the intima. At the site of the tear a thrombus of fibrin and platelets had formed. Serial sections revealed that the vessel was near



Fig 2—A branch of the cystic artery, showing hypertrophy of its wall and marked focal perivascular increase of elastic fibrils and fibrous tissue. Elastica stain, $\times 80$.

the inner surface of the gallbladder. There, the adventitia and media were absent, and only the thickened intima remained. However, farther along, this, too, was involved and partly destroyed by the inflammatory process. No outpouching of the intima was evident. The veins and several arteries in the vicinity were occluded by organized thrombi.

The remaining branches of the cystic artery were all the seat of a process different from that described in the foregoing paragraphs. All of these vessels

showed hypertrophy of the media, proliferation of the intima and an increase of fibrous and elastic tissue of the adventitia. This was considered the result of their being embedded in chronically inflamed tissue. In addition to these changes, however, a more recent process was noted, with a definite sequence of events, since many of the vessels were involved in different stages of the disease. A composite of all the changes answers to the following description, according to progression. The media was edematous and at one point became rarefied as a result of a decrease of muscle fibers and a "stretching" of elastic fibrils. In other places, the media had ruptured, and when the rupture included the intima a thrombus of



Fig 3—A branch of the cystic artery, showing edema and focal rarefaction of media. Note the dense fibrous tissue at the corresponding point in the adventitia. Hemalum and eosin, reduced from $\times 80$.

platelets and leukocytes formed. When the adventitia was also broken, the thrombus, as well as parts of the internal elastic membrane and intima, was found extruded into the perivascular tissue. At times the thrombus became organized, and a spurious aneurysm formed, at other times, small vessels, as they left their site of origin, showed disintegration. Inflammatory cells were absent in the wall or in close proximity about the vessel.

The artery that led to the aneurysm was the seat of a similar process. Here, too, an inflammatory process was lacking.

In the aneurysm, proximally, the intima was markedly thickened, owing to an increase of elastic fibrils and connective tissue and the presence of large branched cells. The lumen was almost occluded as a result of this proliferation. The aneurysmal sac, which was ruptured, was composed of the following layers given in order from the outside inward—a layer of granulation tissue with newly formed capillaries that extended for one-half the distance about the sac and was similar to the granulation tissue of the mucosa of the gallbladder, a thin layer of young connective tissue with fibroblasts, which stained pale reddish pink by van Gieson's method, and which took its origin from the intima, finally, a thick inner coat of



Fig 4—An artery showing rupture of its entire wall, with the formation of an organized thrombus at the site of rupture. Note the segmentation of the internal elastic membrane. Elastica stain, reduced from $\times 80$

laminated layers of fibrin, leukocytes and red cells. The organization became less pronounced as the lumen was approached. The sac was ruptured at the point of its attachment to the wall of the blood vessel.

Several branches of the artery, the site of the origin of which was opposite the aneurysmal sac, showed necrosis, rupture of their walls and formation of thrombi, all as in the process described.

In the cystic artery distal to the aneurysm both inflammatory and degenerative changes were noted as described for the portion proximal to the aneurysm.

PATHOGENESIS

The condition responsible for the changes in the cystic artery and the formation of the aneurysm was undoubtedly the inflammatory process in the wall of the gallbladder. This was both acute and chronic. As a result of the chronic process, the blood vessels lying in the wall of the gallbladder showed marked hyperplastic changes in all their coats. Of special interest was the adventitia, which presented an increase not



Fig. 5—Ruptured aneurysm of a branch of the cystic artery. Hematoxylin and eosin, reduced from $\times 25$.

only of fibrous tissue, but also of elastic fibrils. The acute inflammatory process acted directly on the walls of the blood vessels, eroding or obliterating them.

Many of the vessels, however, were the seat of changes not to be accounted for by the inflammatory lesions. These arteries were embedded in fibrous and elastic tissue and were not infiltrated by inflammatory cells. The changes were degenerative, perhaps as a result of the toxic action of the infected bile. The reaction to this toxic substance

was an edema of the muscularis, which was followed by a rarefaction at one point and finally a rupture

When this tear extended to the intima, a thrombus formed at this site. If the adventitia was also involved, the pressure of the blood forced the thrombus, as well as portions of the intima and internal elastic membrane, into the perivascular tissue.

If the artery was of medium caliber and the process a gradual one, the thrombus at the site of rupture became organized and formed the wall of a spurious aneurysm.

The latter was the mechanism of the formation of the large aneurysm. It was, however, of some duration, for the aneurysm communicated with the lumen of the vessel and can thus be classified as a true aneurysm (Kaufmann,¹¹ Menetrier¹²).

Because the rupture of the aneurysm occurred at its attachment to the arterial wall, it is deduced that the blood pressure within was responsible, rather than a passing stone, as in such a case the most exposed part would have been the site of rupture.

DIFFERENTIATION FROM PERIARTERITIS NODOSA

The resemblance of some of the lesions of the vessels described to periarteritis nodosa warrants a differential diagnosis.

Grossly, the gallbladder in periarteritis nodosa is fairly typical. The mucosa is edematous, discolored a dark brown and at times may be studded with hemorrhagic infarcts. On palpation along the cystic artery spindle-shaped nodules are felt, like a string of pearls (Klotz,² Walter,⁴ Gruber,¹³ Wesemann,¹⁴ Singer¹⁵). Rarely, is the gallbladder the seat of a pyemic process (Walter, Gruber).

In the case reported none of these characteristics was found but instead an acute exacerbation of a chronic cholecystitis and cholelithiasis.

Microscopically, the end-stages of both conditions are similar in that there is occlusion of the vessels by thrombi with organization and formation of aneurysm. The earlier stages however differ appreciably. The process, in both instances begins in the media. In periarteritis nodosa there are edema, fibrinous exudate hyalinization and necrosis of the media. A moderate to extensive infiltration by leukocytes (especially

11 Kaufmann, E. Aneurysms, Philadelphia: P. Blakiston's Son & Company, 1929, vol. 1, p. 132.

12 Menetrier, M. Des Aneurysms, *Arch. de med. exper.* **2**: 97, 1890.

13 Gruber, G. B. Zur pathologische Anatomie der Periarteritis nodosa. *Virchows Arch. f. path. Anat.* **245**: 123, 1923.

14 Wesemann. Ein Fall von Arteritis nodosa, *Inaug. Diss.*, Köln, 1921.

15 Singer, H. A. Periarteritis Nodosa, *Arch. Int. Med.* **39**: 865, 1927.

eosinophils) lymphocytes and plasma cells follows (Gruber,¹³ Arkin¹⁶) Later, the process extends to involve the adventitia and intima. Thrombi and formation of aneurysms are common.

In the case reported, the media was edematous and underwent degenerative and atrophic changes rather than necrotic and inflammatory ones. There was no cellular exudate in the wall of the vessel. (This refers to the vessel in which the aneurysm formed.)

Finally, in periarteritis nodosa, the vessels of more than one organ are involved (Kussmaul and Maier,¹⁷ Gruber,¹³ Klotz,² Walter,⁴ Lemke,¹⁸ Wesemann,¹⁴ Singer¹⁹), although localized cases have been described (Keegan¹⁹).

In the reported case only the cystic artery was involved.

COMMENT

In aneurysms of the hepatic artery and its branches, rupture and exsanguination is a common cause of death (Schmidt²⁰). In about 70 per cent of the cases reported in the literature the patient died in this manner. Rupture into the peritoneal cavity is most common. In the two cases of ruptured aneurysm of the cystic artery rupture was into the gallbladder or into its duct.

In the case reported in this paper, the aneurysm ruptured into the gallbladder and produced enough intracystic pressure to rupture an ulcer of the wall of the gallbladder. Thus an intraperitoneal hemorrhage resulted.

The association of aneurysm of the cystic artery with atrophic cirrhosis of the liver has not been heretofore reported. Three cases of the latter have occurred, however, with aneurysms of the hepatic artery (Ledieu,²¹ Sacquepée,²² Waltzold²³). The etiology given for two of these cases involved syphilitic endarteritis. In the third case the etiology was not given.

16 Arkin, A. Periarteritis Nodosa, *Am J Path* **6** 401, 1930.

17 Kussmaul, A., and Maier, R. Ueber eine bisher nicht beschriebene eigen-thümliche Arterienerkrankung, die mit Morbus Brighti und rapid fortschreitender allgemeiner Muskellähmung einhergeht, *Deutsches Arch f klin Med* **1** 484, 1866.

18 Lemke, R. Ein weiterer Beitrag zur Frage der Periarteritis nodosa, *Virchows Arch f path Anat* **245** 322, 1923.

18 Lemke, R. Ein weiterer Beitrag zur Frage der Periarteritis nodosa, *Arch Int Med* **36** 189, 1925.

20 Schmidt, M. B. Todliche Blutung aus einem Aneurysma der Leberarterie bei Gallensteinen. *Deutsches Arch f klin Med* **52** 536, 1894.

21 Ledieu. Des Aneurysms, *J de med de Bordeaux*, 1856, p. 125.

22 Sacquepée, B. Blutung im Inneren der Leber mit Durchbruch in die Bauchhöhle, *Zentralbl f path Anat* **11** 748, 1900.

23 Waltzold D. Leberruptur mit todlicher Blutung infolge Berstens eines oberflächlichen Aneurysmas, *München med Wchnschr* **53** 2107, 1906.

It is possible that the same inflammatory processes, specific or non-specific, are responsible for the formation of the aneurysm, as well as for the cirrhosis of the liver

CONCLUSIONS

A case of aneurysm of a branch of the cystic artery is reported, which had ruptured into the gallbladder and, in turn, into the abdominal cavity, as a result of ulcerative cholecystitis and cholelithiasis

A toxic, degenerative process of the cystic artery is described as the pathogenesis of the aneurysm. This process consists of an edema of the media, followed by rarefaction and rupture at one point. When the tear extends to the intima, a thrombus forms, which, if the process is slow, becomes organized and forms the wall of an aneurysm. When circulation is established through the aneurysm, the possibility of rupture is great.

THE HISTOLOGY OF EXPERIMENTAL TUBERCULOSIS IN DIFFERENT SPECIES

A COMPARATIVE STUDY

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By the intracerebral method of inoculation described in a previous paper,¹ it is possible to obtain well defined lesions of tuberculosis in the tissues of many animals that are highly resistant to the infection by the ordinary means of exposure. For example, it is practically impossible to induce demonstrable lesions of the disease in chickens by the intravenous or subcutaneous injection of the human or bovine forms of the organism, yet when these forms are injected into the substance of the brain pronounced lesions result in this organ. The guinea-pig, which is very susceptible to infection with the tubercle bacillus of either human or bovine origin by the usual methods of exposure, is extremely resistant to the avian form of the organism. When the guinea-pig is inoculated intracerebrally with organisms of avian origin, definite lesions of tuberculosis are established. Again, the dog, although susceptible to infection with the human and bovine varieties of the tubercle bacillus, is extremely resistant to organisms of avian source when exposed by intrabronchial, intravenous, subcutaneous or intraperitoneal injections, or by feeding.² However, when the bacteria are introduced into the brain through a cranial perforation, definite and extensive tuberculous lesions develop.

As a consequence of the experiments described¹ and of others, I have been able to obtain lesions induced by the three forms of *Mycobacterium tuberculosis* in certain species in which this has heretofore not been possible. The tissues obtained from the respective species have been utilized in a comparative study of the histologic changes to determine whether the character of the host's reaction to the bacillus of tuberculosis is dependent on the form of the organism present (whether human, bovine or avian) or whether the character which the lesions assume is dependent on the species harboring the infection. In other words, does the anatomic nature of tuberculosis in a given

¹ Submitted for publication, Jan 6, 1931

* From the Division of Experimental Surgery and Pathology, the Mayo Foundation

1 Feldman, W. H. Am Rev Tuberc **21** 400, 1930

2 Feldman, W. H. J Am Vet M A **76** 399, 1930

animal differ with the type of organism responsible for the lesions or are the tuberculous lesions in a given animal similar regardless of the source of the organism?

METHODS

All cultures of *Mycobacterium tuberculosis* used for the production of lesions in this study were original strains isolated from human, bovine and avian tissues. The type of the respective strains was challenged by the inoculation of guinea-pigs, rabbits and chickens before the cultures were accepted as suitable for the experiment. In determining the true type of a given organism by inoculation of an animal the following tests of pathogenicity were carried out: (1) Guinea-pigs were inoculated subcutaneously or intraperitoneally and (2) chickens and rabbits were inoculated intravenously. Animals living at the expiration of ninety days were killed for necropsy. All chickens used were previously tested by tuberculin. The degree of susceptibility, as determined by the presence of demonstrable lesions of tuberculosis, is shown in the tabulation.

When the disease was induced by the intracerebral route of inoculation, the method of exposure was the same for all animals. With the animal under ether anesthesia the injection was effected through a small cranial perforation,

Results of Tests for Pathogenicity of the Three Types of the Tubercle Bacillus Employed in the Experiments

Type of Organism	Degree of Infection in Animal Inoculated		
	Guinea Pig	Rabbit	Chicken
Human	+++	+	0
Bovine	+++	+++	0
Avian	0	++	+++

care being taken to minimize the possibility of extraneous contamination. The dosage used varied with the size of the animal, being from 0.1 to 1 cc. of a saline suspension prepared from cultures growing on egg or potato medium. In order to provoke possible lesions most of the suspensions were purposely made rather dense, and an attempt was not made to estimate the number of bacteria present in each cubic centimeter.

Material was selected as soon after death as possible and fixed in 10 per cent neutral formaldehyde solution. After fixation the tissues were embedded in paraffin, and sections were prepared. From each block two series of sections were obtained. One series was stained with hematoxylin and eosin, and the other was treated with carbolfuchsin-hematoxylin by a method previously described.³ Although a large number of different species of animals were used in a series of experiments pertaining to the pathogenicity of the various bacillary forms of *Mycobacterium tuberculosis*, the observations recorded here were confined to the chicken, the guinea-pig, the rabbit and the dog.

PATHOLOGIC ANATOMY

Chicken.—Material was obtained from chickens that had died or had been killed subsequent to an injection of one of the three types of the tubercle bacillus. With the avian strain a fatal tuberculous infec-

tion was obtained by either the intravenous or the intracerebral method of inoculation, but death resulted much earlier by the latter method than by the former. The duration of the disease varied from 3 to 10 weeks, dependent on the method of inoculation used. Since it was impossible to incite demonstrable lesions in the chicken by either the human or the bovine form of the organism by the intravenous or by the subcutaneous method of exposure, the only lesions obtained from the common fowl which were due to either of these strains were those

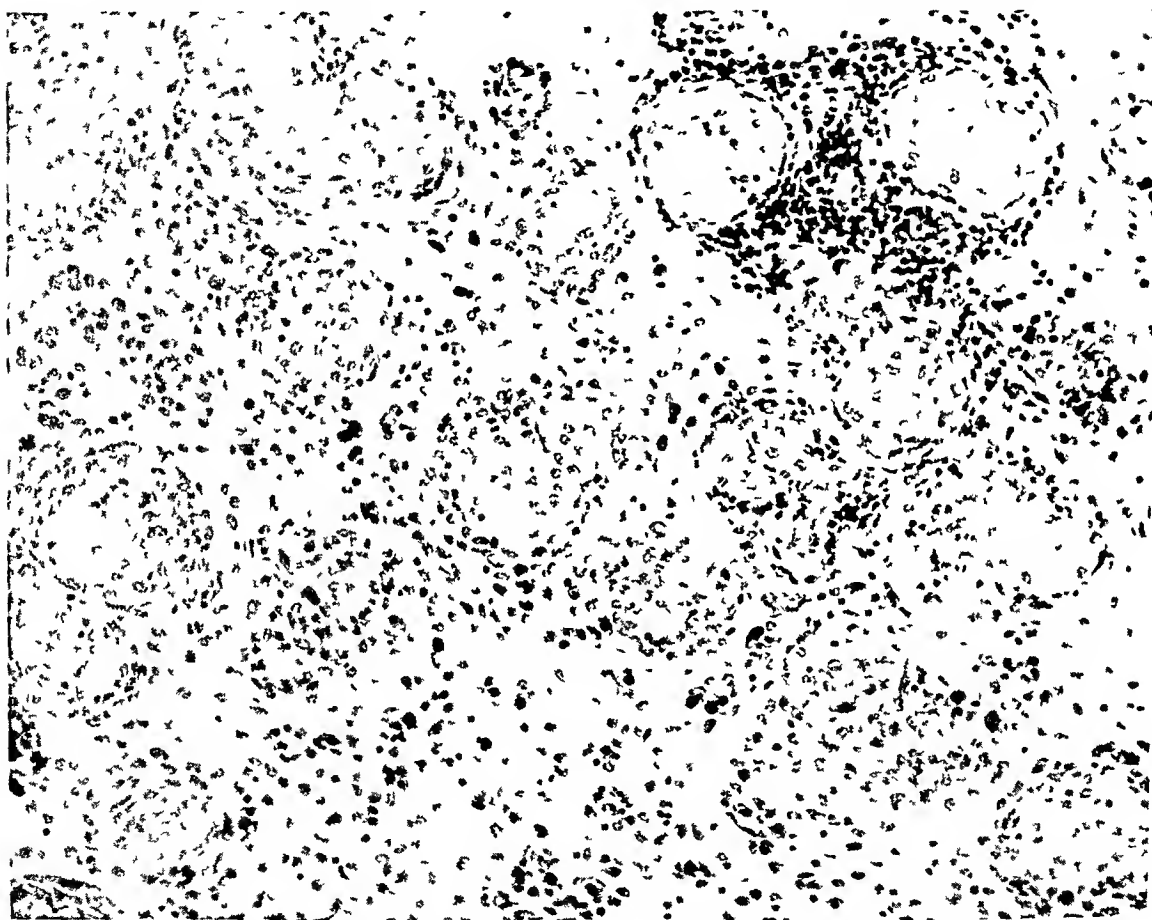


Fig 1—Lesions of tuberculosis in the cerebrum of a chicken. Death occurred twenty-eight days after the intracerebral introduction of the avian organism. The multiple follicular arrangement usually assumed by the monocyctic cells in the tissues of the chicken following an injection with the organism of tuberculosis is shown, $\times 200$

that resulted from the intracerebral method of injection. Of the two birds inoculated in this manner with the organism of human source, one died after a period of 56 days, and the other was killed for necropsy 136 days subsequent to the inoculation. The two that were inoculated with the bacteria of bovine origin were killed for necropsy after 119 days.

In the chickens inoculated intracerebrally with the avian form of the organism lesions were found to be distributed throughout the brain, liver and spleen in such a manner as to indicate a generalized infection. With the human and bovine strains, however, demonstrable lesions were confined to the brain.

A study of the histologic reactions induced in the respective chickens by the three different strains of organisms revealed a remarkable similarity which was strikingly consistent throughout the course of the

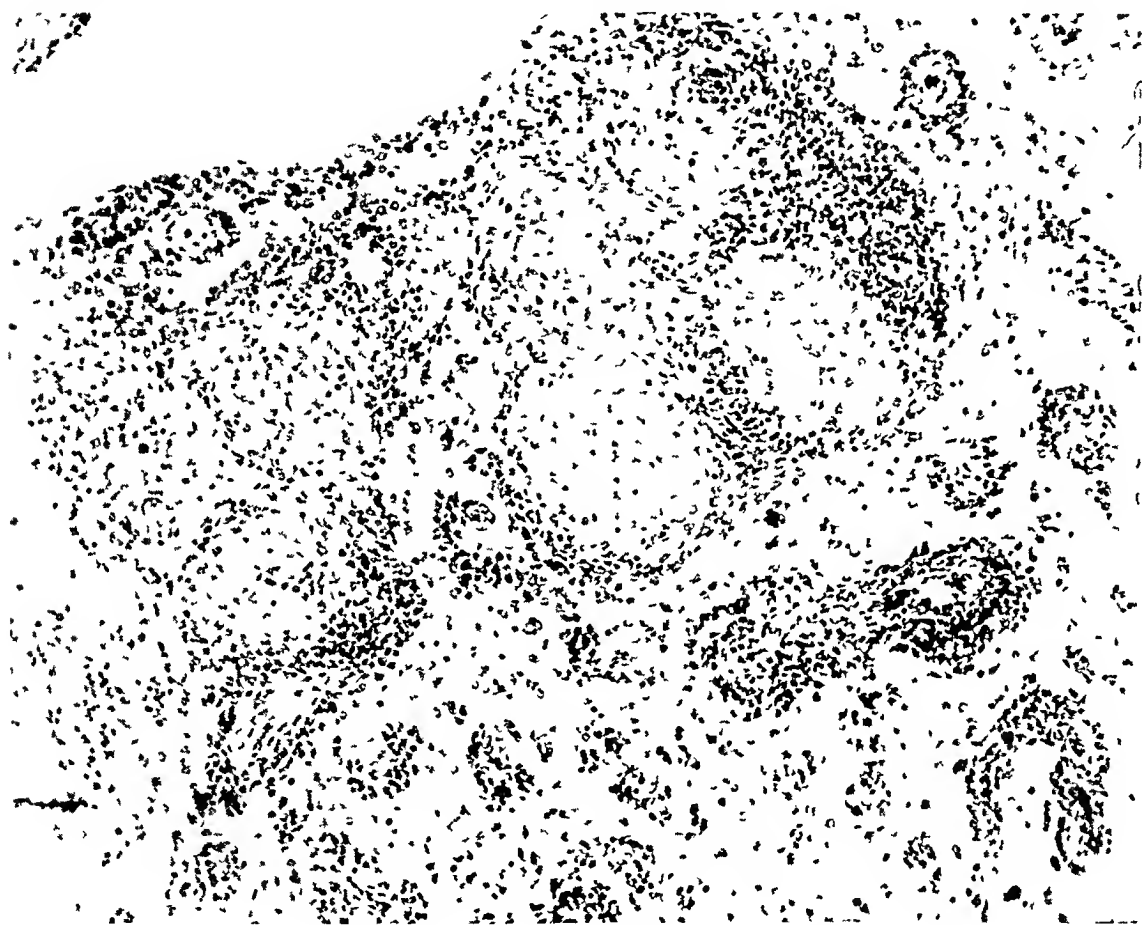


Fig 2—The cellular reaction in the cerebrum of a chicken induced by the intracerebral injection of the human tubercle bacillus. The chicken was killed 136 days subsequent to the injection of the infective material. The monocyctic cells are arranged in circumscribed spherical masses significantly like those in figures 1 and 3.

disease. Regardless of the source of the etiologic agent, the initial cellular response was the same. It consisted of multiple, discrete, spherical collections of monocyctic cells which exhibited a persistent tendency to retain their focal character, even though the amount of infection present stimulated the formation of large numbers of them in masslike formation (figs 1, 2 and 3). The lesions were also charac-

terized, particularly in the early stages, by an attempt at encapsulation. The monocyctic cell constituting the unit of the respective lesions was of a rather large size and exhibited a marked tendency to assume an epithelioid character.

Necrosis seemed to occur at about the same time regardless of the type of the etiologic organism. It was usually of a coagulative or hyaline character and revealed a tendency gradually to become caseous. Necrosis began in the central portions of the respective lesions and

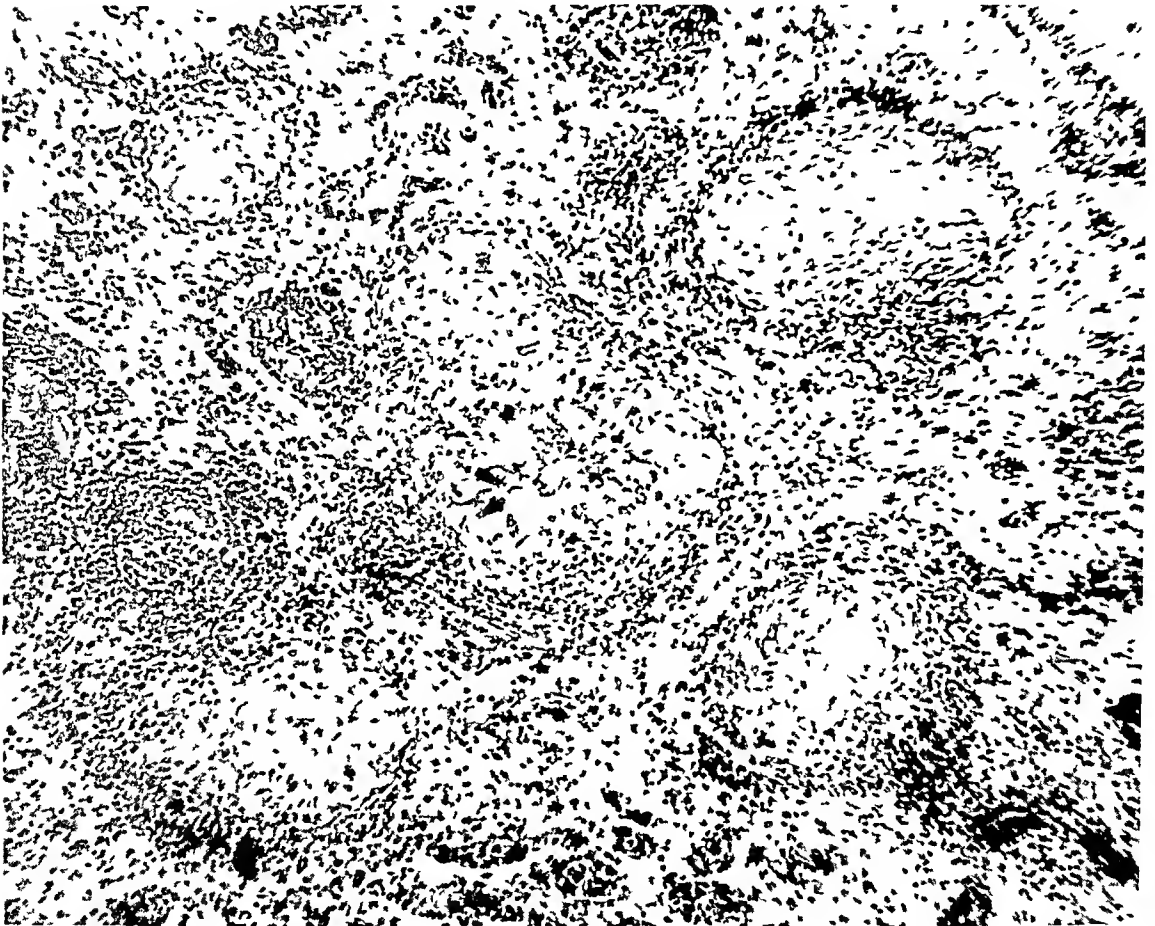


Fig. 3—Multiple tuberculous lesions in the cerebrum of a chicken that was killed 119 days subsequent to the intracerebral injection of the bovine organism. The central lesion had become necrotic, $\times 130$.

progressed peripherally. Calcification, although not prominent in any of the material studied, occasionally appeared. In those lesions in which necrosis was evident the monocyctic cells in contact with the necrobiotic elements were arranged in palisade formation with the long axis of the cells toward the center of the lesions. The nuclei of these cells were situated in the extreme peripheral portion of the cytoplasm, and the opposite ends of the respective cytoplasmic processes merged

imperceptibly with the necrotic cellular detritus. Giant cells of the Langhans type were present in some of the older lesions.

Many of the lesions which had been provoked by the human and bovine forms of the tubercle bacillus revealed peripheral lymphocytic response (figs 2 and 3). This varied in amount from a few cells to a large accumulation, even within the limits of a given section. Variable numbers of acid-fast bacilli were demonstrated within the lesions of all tissues studied. They were most numerous in the earlier lesions and apparently were reduced in number as the duration of the disease was prolonged.

Comment. Tuberculous infection in the tissues of the chicken when induced by any of the three forms of the tubercle bacillus is characterized by the appearance of definitely focal, circumscribed collections of monocyctic or epithelioid cells of a rather large, clear type. The lesions, which are often multiple, may become confluent, but even though a conglomerate tubercle results, the identity of the separate follicle-like masses of epithelioid cells is usually maintained and is discernible.

Guinea-Pig.—It was not possible to provoke demonstrable tuberculosis in the guinea-pig with the organism of avian origin by either the subcutaneous or the intraperitoneal route of inoculation. Lesions, however, were obtained when the bacteria were deposited within the substance of the brain. By the intracerebral method of exposure a tuberculous infection was established which proved fatal in from eighteen to fifty-seven days, with discernible signs of the disease in the brain, liver and spleen and occasionally involvement of the lung. With the human and bovine forms of the bacillus lesions were readily produced by injecting the organisms either subcutaneously or intraperitoneally, death occurring as early as twenty-three days afterward. Animals living at the expiration of eight weeks were killed for necropsy. By the procedure described it was possible to secure with each of the three forms of the bacillus definitely recognizable lesions of comparable duration for the purpose of a comparative study.

The changes established by the respective bacterial strains were practically the same throughout the various animals used in this phase of the study. They differed materially, however, from those induced in the chicken. Instead of the monocyctic cells exhibiting a discrete focal arrangement as in the common fowl, they assumed an entirely different deposition in the guinea-pig. They appeared in the earlier stages in such organs as the liver and the brain as compact, diffuse accumulations with very irregular outlines (figs 4, 5 and 6). In the spleen the lesions in every instance had their inception in the malpighian body, where they expanded peripherally without demonstrable evidence

of encapsulation. The appearance of giant cells of the Langhans type was so inconsistent in the guinea-pig material studied as to make it difficult to interpret the rôle of this cell in the tuberculous reaction. It appeared in some of the lesions of animals that died as early as twenty days after inoculation, although in others in which the lesions were of comparable duration it was not seen. Again it was occasionally present in lesions of from six to eight weeks' duration. A remarkable exhibition of these cells appeared in the liver, spleen and renal lymph



Fig. 4—Cellular reaction ($\times 150$) in the brain of a guinea-pig that died twenty days subsequent to an intracerebral injection of the avian organism. The mononuclear cells are disposed in a diffuse manner. This figure may be contrasted with figure 1.

node of a guinea-pig that died fifty-seven days after intracerebral injection of organisms of avian origin. The interior of each cell unit was filled to capacity with acid-fast bacilli.

As the lesions expanded the central portions of many eventually became necrotic. The necrosis was usually of a caseous nature, although that of coagulative type was occasionally seen. Not infrequently both types were discernible within a single microscopic field. Calcification

was not observed in any of the lesions examined. Acid-fast organisms were demonstrated within the lesions of all tissues studied.

Comment—In the guinea-pig the three types of tubercle bacillus produced lesions which were practically identical in their morphologic aspects. The lesions were characterized in their earlier stages by closely arranged, diffuse masses of mononuclear cells, disposed in an irregular, nonconventional manner, and in this regard they differed materially from the lesions produced by the same organisms in the chicken. Fibrosis



Fig 5—Tuberculous lesion ($\times 150$) in the brain of a guinea-pig that died twenty-three days after an intracerebral inoculation of the human organism. There is no tendency toward tubercle formation such as occurred in the brain of the chicken, shown in figure 2.

or attempted encapsulation was not observed. Necrosis without calcification finally changed the character of many of the separate cellular accumulations although the peculiar palisade arrangement of the cells adjacent to the necrotic tissue which was so evident in the lesions of the chicken, was not seen in the lesions of the guinea-pig.

Rabbit—A tuberculous infection was established in rabbits by the intravenous injection of bacteria representing each of the three different forms of tubercle bacillus. The disease was also produced by the

introduction of each of the three bacillary forms into the substance of the cerebrum, and in one instance it was produced by subcutaneous inoculation of the bovine form of the organism. The duration of the lesions in the respective rabbits varied from 11 to 250 days. The earlier lesions were obtained following intracerebral inoculation, whereas the animals in which lesions were obtained after 250 days were those inoculated intravenously with organisms of human origin and finally killed for necropsy.



Fig 6—Lesion of tuberculosis ($\times 150$) in the brain of a guinea-pig that died twenty days following the intracerebral injection of the bovine organism. The histologic appearance of the cellular reaction is not essentially different from that observed in figures 4 and 5.

Comparison of the individual lesions of comparable duration in the various rabbits showed that there were no essential differences in the character of the histologic reaction to the three forms of the infecting agent (figs 7, 8 and 9). There were, of course, notable differences in the degree or in the extent of the infection due to variations in the inherent susceptibility of the rabbit to the three bacillary forms of the organism. The rabbit is exceedingly vulnerable to organisms of

bovine and avian origin and considerably less so to organisms obtained from human beings. As a consequence one observes differences in the cellular reaction which are indicative of the degree to which the respective organisms are able to express the full measure of their pathogenicity.

In general, however, the lesions were made up of irregular accumulations of monocytic or epithelioid cells, many of which, with the exception of the lesions of the lung, exhibited a marked tendency to undergo early central necrosis. The Langhans type of giant cell was

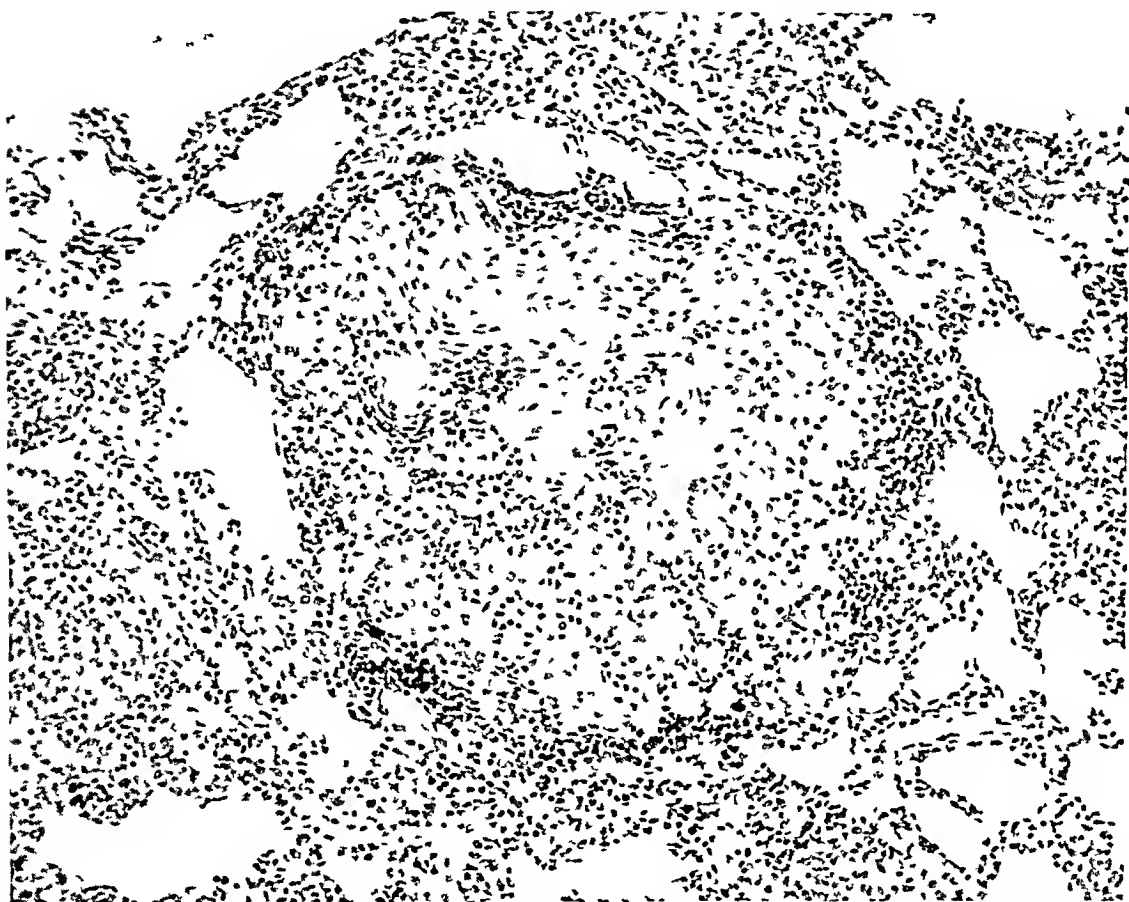


Fig 7—Tuberculous lesion ($\times 150$) in the lung of a rabbit that died ninety-eight days after receiving an intravenous injection of bacilli of avian tuberculosis

frequently present in most of the tissues studied, and many of the lesions of long duration possessed variable amounts of mineral salts. When the disease was rapidly progressive or of long standing, many of the individual cellular units or tubercles showed a tendency to coalesce. In the lungs of those animals in which the disease had continued for a protracted period the formation of abscess with occasional cavitation was observed.

Although there were minor differences in the appearance of some of the lesions in the respective animals the differences were due to the

different anatomic situations in which the lesions appeared rather than to a specific cellular response to the presence of a particular form of *Mycobacterium tuberculosis*. The splenic lesions were confined rather consistently in the early stages to the malpighian bodies, whereas those in the lung, liver and kidney were not restricted by definite anatomic limitations. Many of the lesions of prolonged duration stimulated the production of large numbers of lymphocytic cells, which were present in the zone immediately adjacent to the uninvolved tissues. Connective

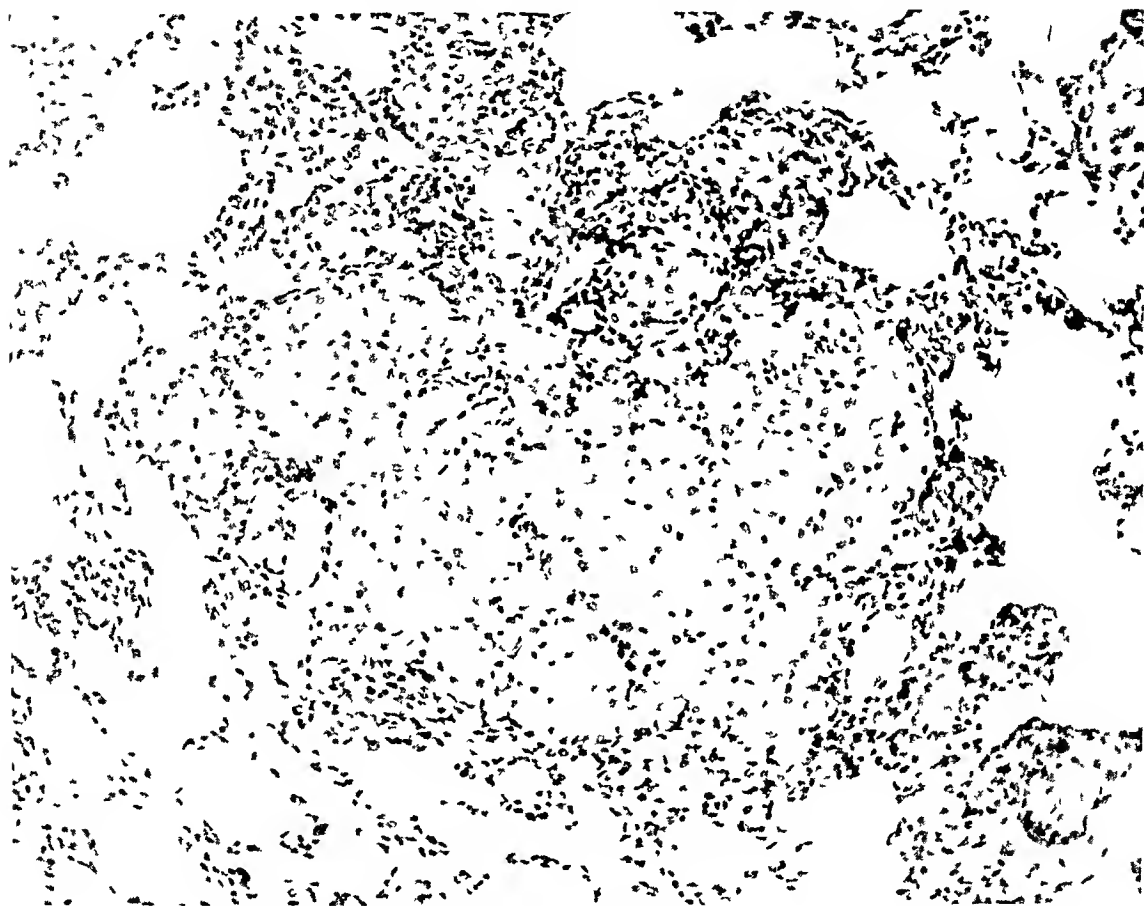


Fig. 8—A focal accumulation of epithelioid cells ($\times 180$) in the lung of a rabbit that was killed 250 days subsequent to an intravenous injection of the human tubercle bacillus

tissue encapsulation or fibrosis was not associated with the lesions in the tissues examined. The cerebral lesions were practically identical, regardless of the source of the infecting organism. They were rather widespread and usually caused the death of the animal within a relatively short time, from eleven days to three weeks. In tissues which were appropriately stained, acid-fast organisms were demonstrated in all lesions studied.

Comment. The lesions of tuberculosis in a series of rabbits following the experimental production of the disease with the three different

forms of the infecting organism were without significant differences (figs 7, 8 and 9). They were characterized by the formation of irregular masses of monocyctic or epithelioid cells, and the central portion of many became caseated within a relatively short time. Giant cells were numerous, and encapsulation was not apparent.

Dog—Lesions of tuberculosis were provoked in dogs by each of the three bacillary forms of the organism when the infective agent was introduced intracerebrally. As previously reported² dogs proved



Fig 9—Tuberculous lesion ($\times 150$) in the lung of a rabbit. Death occurred 154 days after a subcutaneous inoculation of bacilli of bovine tuberculosis.

exceedingly resistant to the avian form of the bacillus by every route of exposure except by way of the brain. Infection established in this way with organisms isolated from a chicken produced lesions in the brain, spinal cord, liver and occasionally in the spleen, the lungs escaped demonstrable involvement in every instance. The human and bovine forms of the tubercle bacillus when injected intracerebrally set up lesions in the lungs, besides those in the liver, brain and spleen. Lesions were also obtained in the lungs and livers of dogs that were inoculated intravenously with bacilli of bovine and human origin.

In dogs, as in the other species used, a fatal tuberculous infection resulted much earlier following the intracerebral introduction of the infection than by the other means used to establish the disease. Those inoculated intracerebrally succumbed in from eighteen to sixty-three days, and those inoculated intravenously survived for a period of seventy-three days or until they were killed for necropsy after one year.

Since the brain and the liver were the only organs to be consistently affected by each of the three forms of the infecting organisms, the comparative study of the resultant lesions was limited to tissues obtained from these organs. A detailed account of the pathologic changes following the exposure of dogs to bacilli of avian tuberculosis has been recorded elsewhere.⁴

When dogs were inoculated with organisms of avian origin the lesions were perhaps somewhat more extensive, and the cerebral tissue was more involved, than when lesions were produced by either the human or bovine forms of the bacillus. With this exception the character of the cellular reaction was essentially the same regardless of the origin of the etiologic bacteria. Even the lapse of time did not materially alter the histologic picture in the respective animals. It persisted as a more or less irregularly diffuse collection of closely packed monocyctic cells without evident encapsulation, but with an occasional appearance of lymphocytic infiltration of the peripheral portion of the lesion. The monocyctic cells did not assume an "epithelioid" appearance. The lesions were situated either just under the pia mater, which they frequently followed into the depths of the sulci, or within the substance of the cerebral tissue. In many of the brains, lesions were present in both situations, and the lesions often appeared to have had a perivascular inception. The formation of concentric, tubercle-like structures or giant cells was not observed. Necrosis of the central portion of some of the lesions induced by the avian organism was observed, and the same retrogression was present to less degree in a few of the lesions that developed as a consequence of the human organism. Calcification was not observed in any of the lesions examined. Acid-fast organisms were present within the lesions of all tissues studied, and from those in which cultures were attempted organisms possessing the usual characteristics of *Mycobacterium tuberculosis* were obtained.

A study of the sections prepared from the livers of dogs that died as a consequence of the intracerebral inoculation of each of the three forms of the tubercle bacillus revealed lesions in which there was no marked dissimilarity. The majority of the lesions, regardless of their

⁴ Feldman, W. H. Am J Path 7:147, 1931.

duration, appeared as ovoid or irregularly spherical masses of monocyctic cells of the same character as those which constituted the lesions in the cerebrum. The lesions, which were numerous, were situated rather promiscuously throughout the liver. In none of them could the formation of a capsular structure be discerned, and giant cells of the Langhans type were absent. Necrosis or calcification was not observed. Acid-fast organisms, although demonstrable, were not numerous, except in one liver in which the lesions had been induced by the intravenous

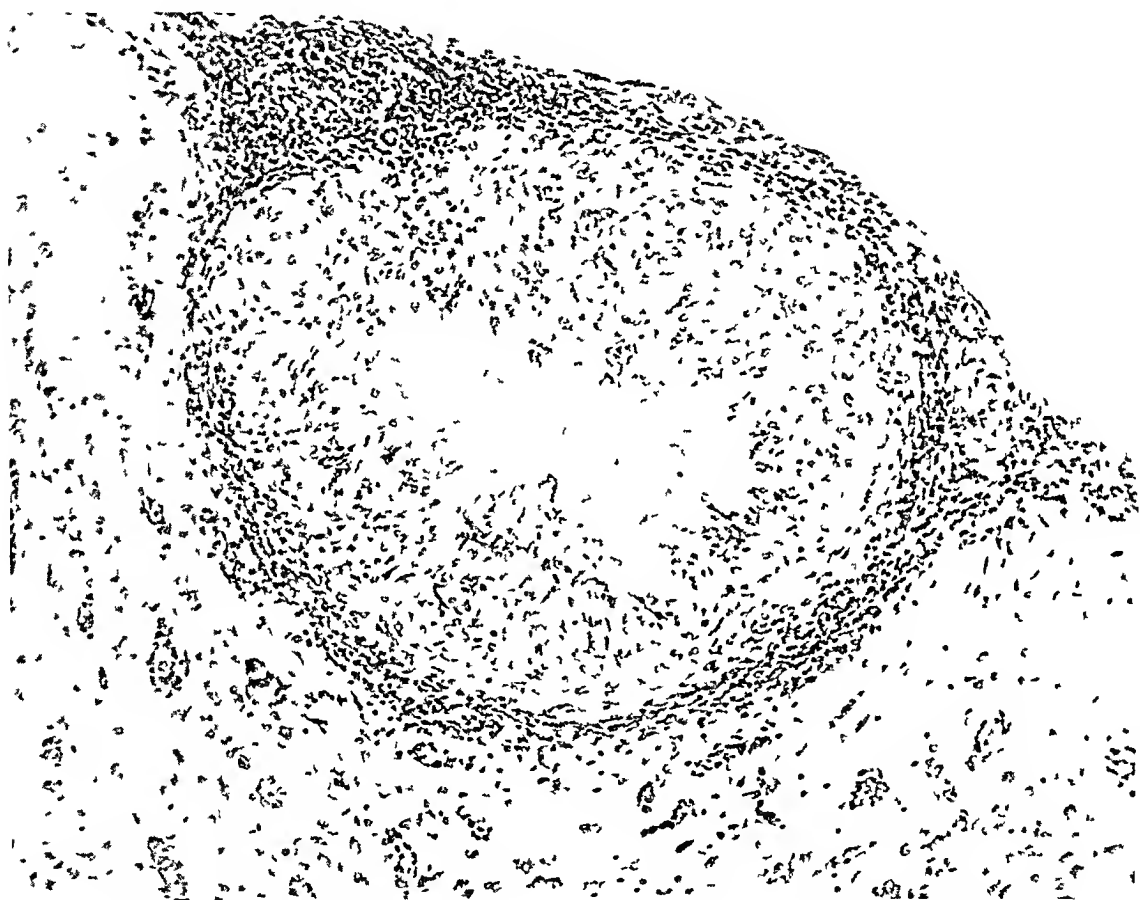


Fig 10—Tubercle ($\times 200$) in the liver of a chicken in a case of spontaneous tuberculous infection. The lesion which is undergoing necrosis, is definitely circumscribed. This figure may be compared with figure 11.

injection of the human form of the organism. The lesions in this instance differed somewhat from the ones I have described in that they were much more extensive. They likewise exhibited less tendency to produce the focal type of cellular formation. Instead, the reaction was diffuse and showed a predilection for the perilobular portions of the organ. In this material an occasional cell form suggestive of the Langhans type of giant cell could be seen, and tremendous numbers of acid-fast bacilli were present.

Comment Lesions produced experimentally in the brains and livers of dogs by each of the three types of the tubercle bacillus were found to be alike, except for a few minor differences which were due, perhaps to certain anatomic peculiarities of the involved organs. The lesions were characterized by the presence of monocytic cells arranged in compact masses without evident encapsulation or typical tubercle formation. The lesions, which were rather extensive and numerous, showed only a slight tendency toward retrogression.

Several tuberculous livers of swine, obtained from abattoirs, also were studied. The lesions were of a multiple, miliary character, and emulsions prepared from the diseased tissue and injected into chickens tested with tuberculin eventually produced extensive lesions of typical avian tuberculosis. Cultures obtained from portions of the original emulsions resembled the avian form of the organism in every way. A comparison of the lesions that occurred in the livers of swine with those which resulted in the livers of the inoculated chickens showed great dissimilarity. As has been mentioned, the lesions in the chicken were like those which are usually seen following a spontaneous tuberculous infection in this animal (fig. 10). The lesions were focal and more or less discrete, with a rather definitely circumscribed, irregularly spherical contour. The lesions in the livers of swine, however, were irregularly diffuse, consistently larger than the lesions of the fowl, and with no discernible effort on the part of the connective tissue elements to establish a zone of demarcation between the cells of the lesions and uninvolved hepatic tissue.

COMMENT

Although these studies have made it possible to observe the reaction of several different species of animals to each of the three varieties of the bacillus of tuberculosis, no claim is made that similar lesions would be found if the disease could be studied following its spontaneous inception in the respective species. The usual chronicity of the infection following its spontaneous induction gives the host an opportunity for a much fuller expression of the protective mechanism than is usually possible following the experimental production of the disease. However, lesions that had existed from three months to one year were sufficiently established in their histologic design to enable one to foresee with some degree of accuracy what the ultimate anatomic reaction was to be. Also it seems logical to assume that significant morphologic differences should become evident rather early in the pathogenesis of the respective lesions, particularly if one considers the nature of the development of the tuberculous process in the common fowl. Although the tubercle is rightly considered the anatomic unit of tuberculous infection, in the chicken it is subject to some histologic variation.

as compared with the lesion in the lower mammals. This became apparent from the fact that each of the three forms of *Mycobacterium tuberculosis* induced lesions in the brains of chickens which were essentially identical, whereas the same bacteria produced in other species, including the rabbit, guinea-pig and dog, lesions which were unlike those produced in chickens.

In general it might be said that the lesions of tuberculosis in the chicken differed from those in mammals by the monocytic cells early

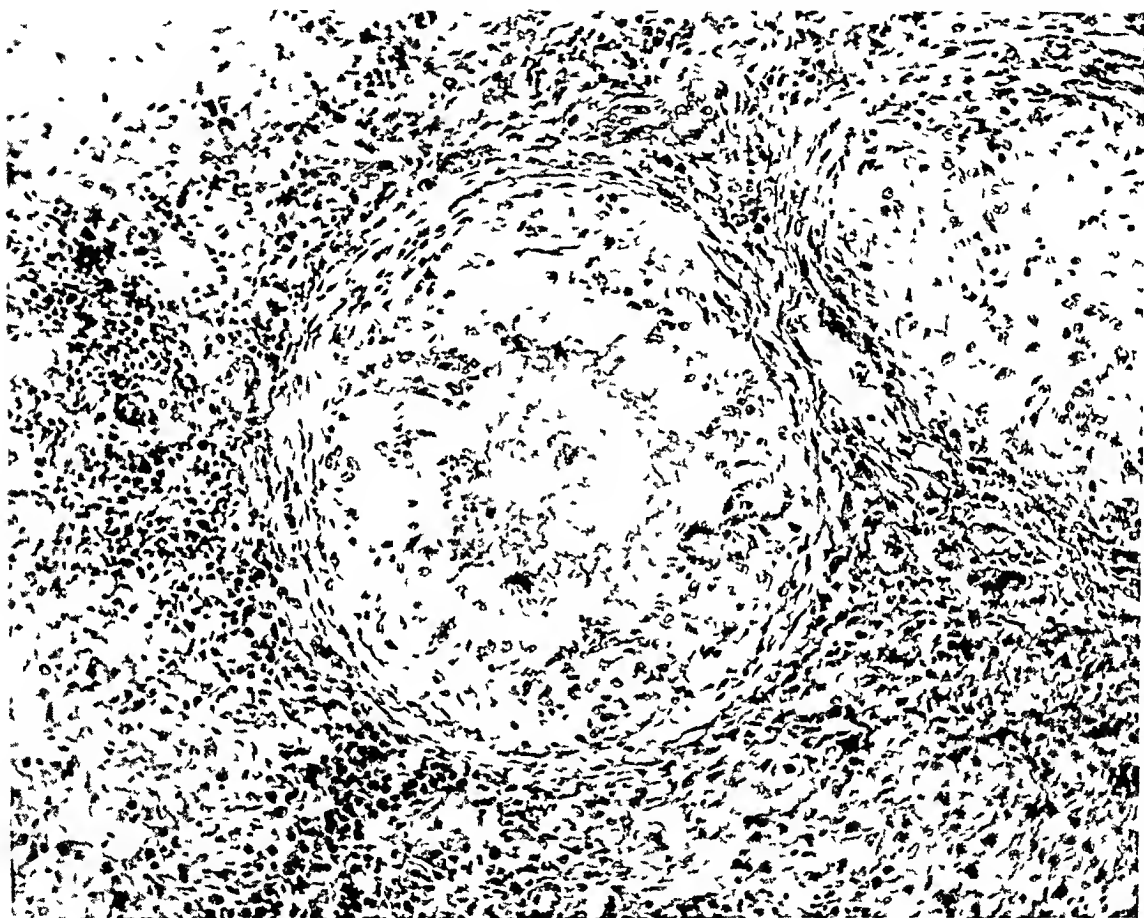


Fig. 11—Solitary tubercle ($\times 150$) near the periphery of the cerebrum of a chicken. The same case is shown in figure 3. The animal was killed 119 days after an intracerebral exposure to bovine tubercle bacilli. This figure may be compared with figures 6, 9 and 10.

assuming an epithelioid character and exhibiting a marked tendency to retain their follicle-like arrangement and to fuse to form conglomerate tubercles. They are also characterized by a definite attempt to become encapsulated and in the older lesions by a peculiar hyalin-like degeneration of the center of the tubercle (fig. 11). I have failed to observe in chickens even in those spontaneously affected with the avian organism,

the atypical or neoplastic-like lesions described by Chretien, Germain and Raymond ⁵

It also appeared from this study that, so far as the various mammals are concerned, the tuberculous process in the respective species studied was without significant differences regardless of the source of origin of the organism used to incite the lesions. This seems of significance and suggests the impossibility of one being able accurately to designate the bacillary type responsible for a given lesion on the basis of a morphologic study alone. It would seem that any differences of histologic detail assumed by the resultant reactions of tissue to the respective types of tubercle bacilli are determined for the most part by factors inherent in the host rather than by the possession by each of the three bacillary forms of certain lesion-inciting constituents which are specific for it. In this connection it is of interest to note that Fox, after a comparative study of tuberculous infection in the lower mammals and man, concluded "The form of tuberculosis as seen in all animal groups is the expression of the peculiar characteristic reaction that each group presents to the infection," ⁶ and "individual peculiarity of an order, family, or genus must play a very large rôle in the inception, development, and result of tuberculous infection" ⁷

These observations emphasize the indispensability of inoculation of an animal in every instance before one can definitely claim that a certain lesion has been caused by a given form of *Mycobacterium tuberculosis*. The designation of the bacillary type responsible for a given lesion can be made with certainty only when the results obtained from proper tests of pathogenicity are available.

SUMMARY AND CONCLUSIONS

With the use of pure strains of *Mycobacterium tuberculosis*, representative of the human, bovine and avian forms of the organism, experimental tuberculous infection was induced by various procedures in chickens, rabbits, guinea-pigs and dogs. From the lesions obtained a comparative study was made to determine whether the anatomic character of the cellular reaction in the respective species varied with the type of the tubercle bacillus used to incite the lesions, or whether the histologic character of the lesions in a given species was constant regardless of the form of tubercle bacillus present. From this study the following conclusions seem pertinent:

⁵ Chretien, Germain, and Raymond. Rev. de la tuberculose (s. 3) **4** 25, 1923.

⁶ Fox, Herbert. J. Am. Vet. M. A. **72** 792, 1928.

⁷ Fox, Herbert. Tr. Nat. A. Prev. Tuberc. **24** 199, 1928.

Variations in the character of the reaction of the tissue to *Mycobacterium tuberculosis* are not determined by the type of the organism per se, but by certain indefinite factors which are inherent in the species possessing the infection

The histologic nature of tuberculous infection in a given species is essentially the same regardless of the form or of the origin of the particular strain of tubercle bacillus responsible for the lesions

The lesions of tuberculosis in the common fowl usually possess certain anatomic characters that distinguish them from tuberculous lesions in the lower mammals

These observations indicate that it would be injudicious to designate a given tuberculous infection as being due to organisms of human, avian or bovine origin in the absence of results of tests for pathogenicity

SPONTANEOUS BILATERAL DECAPSULATION OF THE KIDNEYS

REPORT OF A CASE

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AND
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The kidneys described herein were removed from the body of a white woman, 35 years old, who died in the Presbyterian Hospital in March, 1930

REPORT OF CASE

History—Two years previous to death, the patient came to the hospital complaining of constipation, bleeding hemorrhoids and tenderness in the hypogastrium, all of these complaints being of several years' duration

After an enema of barium and a roentgen examination that demonstrated a constriction of the colon, a diagnosis of carcinoma of the sigmoid portion of the colon was made. The neoplasm was removed, and a lateral anastomosis was made between the proximal and distal ends of the colon.

Nine months later, the patient returned to the hospital because of bleeding from the rectum. The previous anastomosis of the colon was resected, an abdominal colostomy was established, and the rectum was removed through the perineum.

In February, 1930, the patient again returned, complaining of loss of weight, bleeding from the opening produced by colostomy and nausea. The symptoms and physical observations were believed to result from metastases in the abdominal cavity and from partial obstruction of the bowel. The patient lived for one month, and during this period the predominating symptoms were prostration, anorexia and weakness. Only one examination of the urine was made. No albumin and no casts were found, and the specific gravity was 1.008. There was no clinical suspicion of renal insufficiency, and a chemical examination of the blood was not made.

Diagnosis—The clinical diagnosis was metastatic carcinoma of the colon proximal to the opening produced by colostomy, partial intestinal obstruction and secondary anemia.

The anatomic diagnosis was long absence of the sigmoid portion of the colon and rectum, old colostomy, carcinomatous metastases in the periaortic and mesenteric lymph glands, in the pelvic peritoneum and in the ureters and periureteral adipose tissue, partial intestinal obstruction due to fibrous adhesions between the small bowel and the carcinomatous metastases, bilateral obstruction of the ureters, bilateral hydro-ureter and hydronephrosis, bilateral decapsulation of the kidneys, general anemia, marked emaciation and ulcers of the colon due to impacted fecal masses.

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Macroscopic Examination of Kidneys—In the retroperitoneal space on each side there was a large, cystic mass, that on the right side weighed 1,060 Gm and that on the left, 1,085 Gm. At the brim of the pelvis each ureter was invaded by gray, firm tissue like that in the peritoneal covering of the small pelvis. The periureteral adipose tissue was also firm and formed a hard encasement for the ureters to within a few centimeters of the renal pelves. Above the constriction of the ureters at the brim of the small pelvis, the walls were only slightly thickened, gray and opaque, and the average circumference of the lumens was 1.5 cm.

The fluid in each of the perirenal sacs was contained in a single cavity (fig 1), and the fluid was watery and light yellowish brown. Attached to the lining of the sacs and the surfaces of the kidneys there were thin clots of blood, some of it brown and some of it reddish purple.

The alterations in the two sacs and kidneys were identical, so that only one kidney and the wall of the cyst will be described.



Fig 1—Photographs of the two kidneys after fixation in formaldehyde. The capsules have been cut open, thus exposing the two compressed kidneys. Clotted blood is adherent to the surfaces of the kidneys and to the linings of the sacs.

The wall of the cyst on the left side was flexible and translucent. Attached to the outside were adipose tissue and peritoneum and at the superior surface muscle was firmly adherent. In its largest extent, the wall was of paper-like thickness but at the thickest regions where the kidney was embedded deep in the wall and where the diaphragm was attached, the wall was from 7 to 10 mm thick.

The kidney was compressed by the fluid so that its medial surface was flattened against the wall of the sac for from 1 to 2 cm from the hilus. The junction of the lining of the sac with the surface of the kidney appeared to be a continuous membrane. Slight manipulation of the kidney however loosened the two surfaces; the wall of the sac then could be traced to the junction of the renal pelvis with the kidney. At this junction (fig 2) there was a wall of fibrous tissue that varied from a tissue paper-like membrane in a few places to a heavy fibrous

band several millimeters thick, in most places. The material that sealed the medial surface of the kidney to the sac was gelatinous and gray.

The lumen of the renal pelvis was ovoid, and the calices were obliterated, in contradistinction to the usual type of hydronephrosis in which the calices are dilated and extend up into the kidney as saccules. The cavity of the renal pelvis was equivalent to about 50 cc. The wall of the renal pelvis was thin. In most places, the wall of the renal pelvis was firmly joined to the kidney, and the cavity of the sac was separated from the cavity of the renal pelvis by from 2 to 3 mm of firm, fibrous tissue.

The surface of the kidney was smooth, and the capsule was transparent, so that grossly it appeared as if the renal substance were bare. The renal parenchyma was light brown, glistening and bloodless. In cut surfaces, the cortical and medullary markings were regular and distinct.

Microscopic Examination of Kidneys—In sections of the wall of the cyst, made from several regions, there was an abundance of young fibrous tissue. Infil-



Fig. 2—Coronal sections through the left kidney and the wall of the sac illustrate the ovoid shape of the renal pelvis. In the section to the left the thinness of the wall between the lumen of the sac and the renal pelvis is demonstrated.

trations by round cells and new blood vessels were sparse. No distinct type of cell formed a lining. The inner layers of the wall appeared to be edematous. In a few regions, where there were gray plaques in the peritoneal covering, carcinomatous metastases were present.

The alterations in the kidneys were slight. The interstitial tissue, particularly of the medulla, was widened, but there was no increase of cells. Near some of the larger blood vessels at the junction of cortex and medulla, and also beneath the capsule of the kidney, there were spaces surrounded by fibrous tissue that contained a homogeneous, eosin-staining material. Covering the kidney, there was a fibrous capsule made up of several layers of fibrous tissue.

In the fat about the ureters there were abundant metastases. The epithelial cells were arranged in solid masses of from 10 to 50 cells, and in a few places formed alveoli.

In sections through the pedicle of the kidney there was no evidence of metastasis

Histologic Diagnosis—The histologic diagnosis was adenocarcinomatous metastases in the wall of the ureters, in the periureteral adipose tissue and in the peritoneum covering the perirenal cyst, dilated lymph spaces between the capsule of the kidney and the kidney itself and also in the renal parenchyma

COMMENT

In the medical literature there are only a few reports of accumulation of fluid in the renal capsule similar to that described here. The alterations that occur with decapsulation from hemorrhage of traumatic origin have been frequently described and are well known.

Except for two instances, fluid that collects in the renal capsule has been regarded as a serous exudate from an inflamed capsule or as lymph from a blocking of the lymphatic channels of the kidney and capsule.

The reasons in favor of interpreting the fluid as having an origin other than from urinary excretion are dependent on chemical examinations and the failure to find an opening between the renal pelvis and the sac outside of the kidney.

Thus far, three names have been applied to this anatomic alteration: perirenal hydronephrosis, perirenal hygioma and renis hydrocele.

Minkowski¹ had the opportunity of investigating the characteristics of the fluid in a perirenal cyst of this type during the lifetime of the patient. A cystic mass, thought to be a hydronephrosis, was observed in the right side of a young man, and fluid was aspirated. This fluid and the urine did not have the same chemical composition, and therefore certain experiments were performed to determine whether or not the composition of the aspirated fluid could be changed with alteration of the chemical components of the urine.

The patient was fed benzoic acid. Hippuric acid appeared in the urine, but not in the cystic fluid. Large doses of methylene blue were administered by mouth. The fluid in the sac became slightly tinged, but not with the same intensity of blue that appeared in the urine. The excretion of urine by the kidney was of normal amount, but nevertheless the sac refilled rapidly after aspiration.

The kidney and its external cyst were removed. In gross relationship of kidney and perirenal hydronephrosis the specimen was similar to ours, except that there was no true hydronephrosis. There was no opening between the renal pelvis and the external sac. Minkowski believed that the fluid was of lymphatic origin due to stasis within the kidney. A thin capsule was present on the surface of the kidney, but he inferred that this had formed after the original space had developed.

¹ Minkowski, O. Mitt a. d. Grenzgeb. d. Med. u. Chir. **16**: 260, 1906.

In other words, the fluid in the subcapsular space was a retrograde flow of lymph from the kidney into the true subcapsular space

Similar specimens have been reported on by Lipschutz,² Hildebrand,³ Connerth,⁴ Coenen and Silberberg,⁵ Malherbe,⁶ Kirmisson,⁷ Good,⁸ Krogius⁹ and Lowenstein¹⁰

Lipschutz and Coenen and Silberberg concurred with Minkowski in holding that the fluid outside of the kidney had its origin from lymph. They believed, however, that the fluid collected within the capsule of the kidney, thus splitting the capsule into two layers.

Hildebrand, because of a bloody fluid in the cyst that he described, and also because of a history of trauma to the patient, believed that a hemorrhage had occurred first, and that subsequently a serous fluid collected. Malherbe also subscribed to this explanation in reporting his case.

In the kidney described by Good, there was a tract between an internal hydronephrosis and the sac outside of the kidney. Kirmisson also believed the fluid in the perirenal space to be of urinary origin, even though he was unable to demonstrate a connection between the renal pelvis and the sac outside of the kidney.

Others have ascribed inflammation of the capsule of the kidney as the cause of the perirenal subcapsular collection of fluid.

In our case, at the time of the autopsy, it was assumed, because of the constriction of the ureters by carcinomatous metastases, that the collection of fluid outside of the kidneys was due to extravasation of urine. The two specimens were viewed from the standpoint of valuable material for a museum rather than with the knowledge that there existed in the literature the conception of lymph stasis as the probable cause.

The chief purpose in presenting the material, therefore, is to demonstrate an unusual disease of the kidney and its capsules.

There is some evidence to support each of the two views, namely, that the fluid is lymph and that the fluid is extravasated urine.

There is no blocking of the lymph channels of the renal pedicle by carcinomatous metastases, and it is through the pedicle that most of the lymph is drained from the kidney and its capsule.

2 Lipschutz, B. *Ann Surg* **81** 502, 1925

3 Hildebrand, O. *Arch f klin Chir* **130** 337, 1924

4 Connerth, O. *Ztschr f urol Chir* **11** 169, 1923

5 Coenen H. and Silberberg, M. *Beitr z klin Chir* **130** 374, 1924

6 Malherbe, A. *Ann d mal de org genito-urin* **8** 268, 1890

7 Kirmisson, M. *Rev de chir* **19** 825, 1899

8 Good. *M & S Rep* **24** 287, 1871

9 Krogius, A. *Finska lak-sallsk handl* **63** 493 1921

10 Lowenstein, E. *Berl klin Wchnschr* **57** 1177, 1920

In some regions, the renal pelvis is separated from the perirenal sac by a tissue paper-like membrane through which one can conceive that urine could filter.

The disease was bilateral and symmetrical. In view of this characteristic, one must bear in mind that there may have been a congenital anomaly in the development of the renal pelvis at its junction with the kidneys. Obstruction of the ureters, with and without carcinomatous infiltration of the lymphatics of the ureter and renal pedicle, is common, yet large collections of fluid in the renal capsule are rare.

The fluid in the perirenal sacs was watery and did not coagulate in fixing fluid.

SUMMARY

Two kidneys with a watery fluid in their capsules are described. The names commonly given to this condition are perirenal hydronephrosis, perirenal hygroma and renal hydrocele.

In the cases of accumulations of fluid in the capsules of the kidneys thus far reported in the literature the accumulations are explained by the authors as collections of lymph from blockage of lymph channels, as exudates from inflammation of the renal capsules, or from hemorrhage, and as extravasations of urine.

The gross and histologic evidence in our case points as much to extravasation of urine within the capsules of the kidneys as it does to blockage of lymph channels. The alterations in the capsule are those of encapsulation, and inflammation seems to be a remote etiologic explanation.

Laboratory Methods and Technical Notes

A RAPID AND PERMANENT METHOD FOR STAINING MYELIN SHEATHS *

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AND

ARAM KRAJIAN

LOS ANGELES

The study of myelinated nerve fibers from the standpoint of pathologic changes, as well as from that of their normal structure and distribution, has been complicated by the length of time required by the various technical methods devised for their successful demonstration. The modifications of Weigert's original method, as well as others more recently described, require considerable time, and often the results leave much to be desired. Weil¹ recently devised a rapid method which serves a useful purpose, although in our hands, it has failed to demonstrate individual fibers as well as we should like. We have devised a method which seems to have many of the advantages of the longer methods, as far as the results obtained are concerned, and yet can be completed in thirty minutes. This is of special value in making a rapid diagnosis of questionable cases in which systemic disease of the spinal cord is suspected. The pathologist may have a section for study by the time he has completed the postmortem examination, for preparations from fresh tissue can be made in even less time than that stated. The stain is permanent as far as can be determined, for we have well preserved sections that were made over a year ago. The details of the fibers are fairly sharp and clear, although not stained as deeply as in the longer methods.

METHOD

Hardening—For rapid diagnosis on fresh tissue, boil the blocks for one minute in 10 per cent formaldehyde and then leave in the same solution in a paraffin oven for five minutes before cutting frozen sections. When the section is not demanded in a short time, fix the tissues in 10 per cent formaldehyde for twenty-four hours or longer.

Sections—Cut frozen sections 10 microns thick. Receive sections in a large dish containing tap water.

Mounting—Draw sections on to slides and let the excess water drain off for about a minute and dehydrate with absolute alcohol, pouring on a few drops two or three times, each time allowing it to evaporate. Blot and dip the slide in a thin

* Submitted for publication, Dec 19, 1930

* From the Department of Pathology, Los Angeles County General Hospital

1 Weil Arthur. A Rapid Method for Staining Myelin Sheaths, Arch Neurol & Psychiat 20 392, 1928

celloidin solution having the section to the slide. Dip the slide in tap water for a few seconds.

Mordanting—Cover the section with 15 per cent hot aqueous solution of ferric chloride² for five minutes. Drain the solution from the slide. Do not wash.

Staining—Cover section for five minutes with equal parts of hematoxylin solution³ and distilled water, heated to 60 C. This stains the section extremely black.

Washing—Wash thoroughly in tap water.

Destaining—Remove excess stain in a 1 per cent aqueous solution of ferric chloride, dipping the slide in and out of the solution until the gray matter begins to appear in contrast to the dark medullary substance. This takes place in from ten to twenty-five seconds.

Washing—Wash the slide quickly in tap water.

Differentiation—Cover the section with a 0.25 per cent aqueous solution of potassium permanganate and shake with the fingers to secure even differentiation, which takes place in about five seconds. This step should be controlled under the microscope.

Washing—Thoroughly wash the section in tap water.

Dehydration—Remove water from the section after draining off the excess by pouring on a few drops of absolute alcohol and draining off, repeating three or four times. Blot between filter paper.

Cleaning—Plunge section in a container of equal parts of aniline oil and xylene for about three minutes and then in xylene for another three minutes.

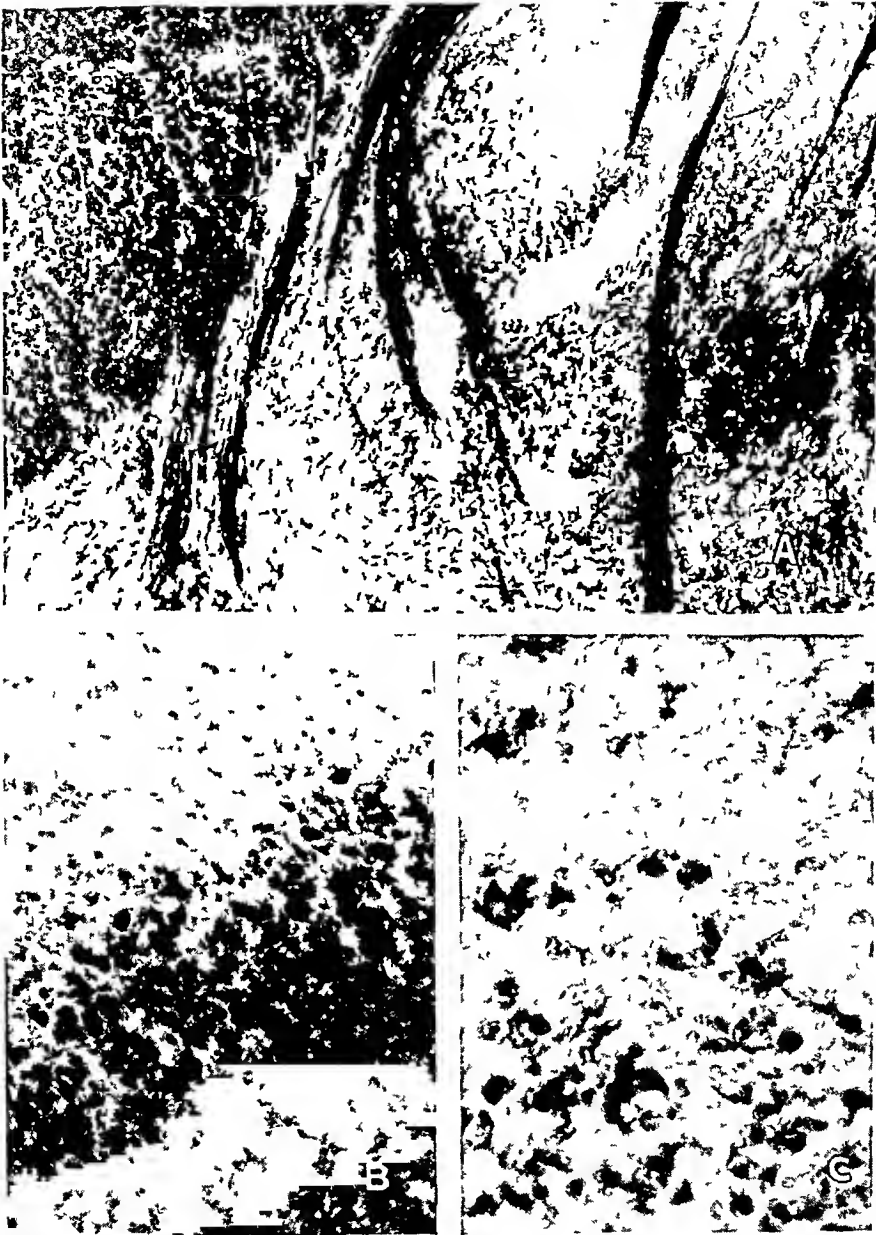
Mounting—Mount in Canada balsam or gum damar.

This method consists essentially of a staining of the myelin sheaths with hematoxylin after mordanting in ferric chloride solution.

The use of hot solution hastens the process and makes it adaptable for rapid diagnosis. The important steps are the removal of excess stain with a 1 per cent aqueous solution of ferric chloride and differentiation in 0.25 per cent aqueous solution of potassium permanganate. If, in the process of differentiation, the black color is too intense, the sections should be destained a little longer in the ferric chloride solution. The process of differentiation serves two other purposes, that of counterstaining the gray matter and degenerated areas a golden yellow and that of checking the action of ferric chloride. This insures the preservation of the stain in the myelin sheath, making a permanent preparation. If after differentiation it is found that the yellow counter stain is not deep enough, the potassium permanganate solution may be added again and the slide shaken for a few additional seconds.

² Ferric chloride solution should be made up fresh each time. Dissolve 15 Gm. of ferric chloride in 100 cc. of hot tap water and raise the temperature to 60 C. just before use.

³ Hematoxylin solution is prepared by dissolving 10 Gm. of hematoxylin crystals in 90 cc. of absolute alcohol and ripening in an incubator at 37 C. for two or three weeks. This solution is stable and will keep for months.



A, myelinated fibers entering the posterior horn of the spinal cord. The method shows them as clearcut fibers in longitudinal section and as well defined rings in cross-section, $\times 100$. *B*, degeneration of the myelin sheaths of the subcortical white substance in a case of encephalitis periaxialis diffusa (Schilder's disease) as demonstrated by the method, $\times 230$. *C*, degeneration of myelin sheaths of nerve fibers at the margin of the fasciculus gracilis in a case of tabes dorsalis, $\times 230$.

The interpretation of the results is the same as in the Pal-Weigert method. The myelin sheath stands out as a ringlike structure surrounding the unstained axis cylinder core as seen in the cross-section. In longitudinal section, it appears as a light-bluish strand observed characteristically in the gray matter of the cord (see figure, *A*) and the deeper layers of the cerebral cortex. The accompanying illustrations show the details emphasized by the method. In rapid degenerations the myelin is seen to be broken up into globules in the course of the nerve fibers (*B*). If the process is a slower one, as in tabes dorsalis, the typical shrinking and distortion of the fibers may be seen (*C*).

The method seems to be best adapted for frozen sections, for we have had poor results on paraffin sections of formaldehyde-fixed material. No results were obtained on tissues fixed in Zenker's fluid.

General Review

REVIEW OF SOME RECENT BOOKS ON BACTERIOLOGY

S BAYNE-JONES, M D

ROCHESTER, N Y

Even in the biologic sciences, "of making many books there is no end" There are, however, peculiar periodic rises and falls in the tide of book-making Granted the constant possibility of publication, the meaning of these ups and downs in the printing of volumes could be determined with assurance only after an examination of all the complicated factors influencing intellectual activity and its expression Without making such a profound analysis, it may be said that one source of influence is certainly the stage of development of a science It would, in the first place, be incorrect to suppose that the absence of book-making indicated stagnation in a science On the contrary, book-making in a science is apt to decrease during periods of intense explorative investigation, when real beginnings are being made After that period, the publication of volumes setting forth the newly acquired knowledge marks a sort of official opening of the new era A second stage of relative stability in a science is often marked by the publication of numerous volumes, either as encyclopedic summaries of collected knowledge or as the exposition of a hypothesis drawn from many singular instances A third stage also, a stage of stagnation, may be remarkable for the publication of numerous monumental volumes expressing the final doctrines of accepted authority

At least two influences obscure these relationships of the publication of books to the stages of development of a science The first of these is the irregularity of activities within the domain of the science All stages from exploration to stagnation may occur at one time, and introductory books will be published simultaneously with the volumes of encyclopedias and documented dogma The second influence obscuring this relationship is that exerted by the increase in journals In earlier times, before there were many journals, publication of original observations in a volume was frequently the first means of dissemination of new knowledge In more recent times, the increase in journals gives the author the means of publishing as separate articles the papers

that in other days he would have assembled first in a book. Finally, the accounts of some experiments, filling all the hundred or more pages in a single issue of a journal, are so voluminous that they should in reality be regarded as books.

During the past five years, there has been an extraordinary increase in the making of books in the science of bacteriology. These books represent all stages of activity in this field. Few or none may be said to express the absolutism of authority, because no one dares to assume authority in these days of incessant critical experimentation, because dogmatism is unfashionable, or because most textbooks contain a sufficiency of dogmatism more or less subtly intruded through an author's subconscious bias or point of view. Many of these books are stimulating for their new conceptions, and many are extremely valuable as sources of reference. Indeed, the bacteriologist has never before been so thoroughly supplied with literary tools for excavation and construction in his fields. It would be profitable to attempt to review and classify all of these books. They are so numerous and varied that a book about books, like Dible's recent monograph, "Recent Advances in Bacteriology," would be required to do justice to all of them. But the reviewer has little more than titular acquaintance with many of them, and is forced by limitations of knowledge and occupation to restrict his review to brief comments on a few books that he has read or consulted.

The rapid extension of bacteriology, its extraordinary utility and the segregation of workers intensely occupied in different parts of the domain have caused the publication of infinitely detailed reports on special regions with little or no coordinated description of the whole. Therefore there is no encyclopedia of bacteriology. While these special publications have great value, it is to be regretted that there is no systematic treatise on the whole field of bacteriology. The longer such a publication is delayed, the longer will each bacteriologic specialist continue to behave as if the bacteria were unique micro-organisms of his province. This attitude has and will continue to hinder the development of a unified general science of microbiology.

In the medical field, the great encyclopedia of bacteriology has been the "Handbuch der pathogenen Mikroorganismen," which Kolle and Wassermann began to publish in 1902. During the past four years, Kolle, Kraus and Uhlenhuth, as editors, have been issuing the fascicles that will compose the ten volumes of the third edition of this "handbook." Each volume contains 1,000 or more pages. At this date, nine of the volumes are complete, while only two sections of the third volume and the general index remain to be issued. The whole work is the product of the labors of more than 150 authors.

An attempt at coordination has been made occasionally, but each chapter is in reality an independent monograph by a specialist in that subject. With a few notable exceptions, the authors are German or Austrian. This, undoubtedly, has some influence on the point of view and the use of foreign literature. In spite of it, however, most of the chapters show an unusual breadth of treatment and an attention to important articles in English, French and American journals. The plan of this great work has been to cover the whole field of microbiology and the disciplines closely related to it—immunology, serologic diagnosis, serotherapy and chemotherapy. Somewhat more than five of the ten volumes are given to bacteriology in nearly all of its phases. The chief emphasis is on the pathogenic bacteria. The short sections devoted to the bacteria of air, soil and water are largely technical and diagnostic. Large parts of several volumes are devoted to pathogenic fungi, spirochetes, viruses, protozoa and helminths. All the traditional aspects of immunology and serology are dealt with, and chapters, such as Landsteiner's on the lipoids, are allotted to the newer biochemical developments in immunology. It is impossible to review this encyclopedia in detail. It may be said, in general, that this third edition preserves the record of older knowledge and brings the summary of newer knowledge well up to date in most of the divisions of medical bacteriology. It is a huge storehouse of facts and suggestions. It is to be hoped that the greatest usefulness of the work will be ensured by the publication of a really good index.

A great compendium of modern knowledge of medical bacteriology is being published in the English language by the Medical Research Council of Great Britain. This work, entitled "A System of Bacteriology in Relation to Medicine," is to be issued in nine volumes, of which volumes 1, 2, 3, 4, 5, 6 and 7 have appeared. This "system" is said not to be an encyclopedia, but a comprehensive survey of the present knowledge of bacteria, spirochetes, filtrable viruses and pathogenic fungi with special regard to their relations to various fields of medicine. It is frankly a system of medical bacteriology, with "short reviews of those economic applications of bacteriology which have special interest for the medical worker." This "system" will be the assembled contributions of nearly 100 British bacteriologists, each a specialist in the subject about which he writes. Unequal treatment and some unsystematic arrangements result from the separate endeavors of a multiplicity of authors. But in this work there is abundant evidence of the coordinating activities of skilful and learned editors. The quality of the volumes has exceeded the high expectations excited by the prospectus of the work. There is no work comparable to this "system" in the English language and I think that no other treatise on modern bac-

teriology is its equal Throughout the work, there is a manifest interest in the bacteria themselves In fact, the whole of the first volume is given to considerations of bacterial morphology, bacterial metabolism, growth and reproduction, life cycles and variation Even in the other volumes dealing with the relationships of bacteria to specific diseases of man, animals, plants and insects there is a continued focusing of attention on the essential characteristics of the micro-organisms Volume 6, which has just appeared, is devoted chiefly to a systematic consideration of immunology, which, however large its own independent serologic scope may be, remains indissolubly attached to bacteriology It would be difficult to overstate the value of this work English and American bacteriologists and the bacteriologists of other countries will for a long time owe a debt of gratitude to the Medical Research Council for the publication of "A System of Bacteriology in Relation to Medicine" At present, while many are profiting by the unindexed volumes, they are hoping that the final publication of a detailed index will give them further cause for thankfulness

Next to these comprehensive, semi-encyclopedic works, come the textbooks of bacteriology as sources of instruction for the novice and as sources of reference or of controversy for the specialist Most of the commonly used American textbooks of bacteriology have been revised and issued in new editions during the past few years The recent editions of Zinsser's "Text-Book of Bacteriology," of the book on "Pathogenic Microorganisms" by Park, Williams and Krumwiede, of Kendall's "Bacteriology" and of Jordan's "General Bacteriology" have brought these books as nearly up to date as the thoroughness of the revisers and the exigencies of publication permit It is remarkable that textbooks dealing with the same general material should be as different as these books seem to be They are, after all, a reflection of the interests and experience of their authors Each book has its excellences and defects, and all suffer from the impossibility of cramping bacteriology, immunology and serology, medical mycology, virology and sometimes protozoology between the covers of one volume of from 700 to 1,000 pages In my opinion, Zinsser's book is to be preferred for its treatment of bacteria in relation to disease, the Park, Williams and Krumwiede book for its description of practical technical procedures and some aspects of public health bacteriology, and Kendall's book for its chemical and metabolic considerations A newcomer in this group is the "Text-Book of Bacteriology" by W W Ford, published in 1928 The special feature of this book is the systematic description of the characteristics of a great number of bacteria and other organisms—micro-organisms of air soil and water, as well as micro-organisms of medical importance The spirochetes, rickettsiae

and filtrable viruses are included in the descriptions, and the book contains chapters on infection, immunity and serology. Its closely printed pages, which number 1,000, contain a wealth of recorded observations, and its illustrations, many of them drawings are refreshingly new. It seems likely that this book will prove of more value to the systematic bacteriologist than to the beginning student.

The latest textbook in the field of medical bacteriology deserves separate consideration in recognition of its individual excellence. This is the two volume work, "The Principles of Bacteriology and Immunity," by Topley and Wilson, published in 1929. The book grew out of the experience of the authors in attempting to provide adequate training for men and women who required a larger course in bacteriology than that given in medical schools in England. The authors attempted, as they have stated, to provide a "text-book which will be of service to those students of medicine and biology who wish to make a serious study of bacteriology and its application to the problems of infection and resistance." They have succeeded admirably in writing the first really comprehensive textbook of medical bacteriology in the English language, in providing students of biology with an adequate treatise on medical bacteriology and in giving medical students a biologically conceived textbook of appropriate bacteriology. In order to accomplish this, the authors required the space of two volumes with a total of about 1,300 pages and were forced to omit all detailed description of technic. The descriptions of technical procedures, which vary from one laboratory to another, are easily supplied in manuals. It seems to me well to free a book from these encumbering descriptions, and I judge from the reception of this book by my associates and students that appreciation of its merits has not been decreased by the absence of the usual pages on technic. Each volume is divided into two parts. In the first part of volume 1, the general characteristics of bacteria are described and discussed in the light of modern discoveries. The second part of the first volume is given to systematic bacteriology. In this section, succinct detailed descriptions of many micro-organisms, chiefly pathogenic bacteria, are provided. The descriptions include also organisms of the azotobacter group and other non-pathogens. Spirochetes, filtrable viruses and rickettsiae are considered here so far as specific knowledge of them permits description. Mycology is not dealt with. The terminology used is the nomenclature, occasionally modified, recommended in the 1920 report of the first American Committee of the Society of American Bacteriologists. Volume 2, part 3, deals with infection and resistance, immunology and serology. Volume 2, part 4, devoted to the application of bacteriology to medicine and hygiene, contains concise descriptions of important infectious dis-

eases of man and animals and of the most significant bacterial phenomena associated with these diseases. There is so much to praise in these volumes that a review might well become an abstract of the book. The intelligence, the critical biologic point of view, the conciseness of style and the choice and arrangement of material shown in this book give it qualities outranking any other book of its kind known to me.

The knowledge of the physiology, metabolism and biochemistry of bacteria has been collected and systematized in several unusual books published during this period. The most comprehensive of these is the three-volume work, "The Physiology and Biochemistry of Bacteria," published in the period 1928-1930 by Buchanan and Fulmer. These volumes are an exposition of the analysis of bacteriologic data by methods of physical chemistry and mathematics. It is amazing to the medical bacteriologist to find that so many bacterial phenomena lend themselves to investigation by these methods and to see in these books so much evidence of the rational physical chemical and biochemical trend in the science of bacteriology. The first volume deals mathematically and descriptively with curves of growth, the phenomena of reproduction and the energetics of cells. The second volume is given to the effects of environment on bacteria and the third to the effects of bacteria on environment. The chemist has criticized these books as being abbreviated compendiums of texts in physical chemistry. The bacteriologist, however, will find this an assistance rather than a hindrance. Throughout, the authors have been concerned with the application of physics, chemistry and mathematics to the understanding of bacterial phenomena. On first inspection, these books appear to have little direct bearing on medical bacteriology. But any one who wishes to see medical bacteriology escape from the fetters of a diagnostic aid knows that its scientific advancement must take off from the fundamental knowledge presented in such books as these.

Somewhat similar material has been handled by Stephenson in a single volume, "Bacterial Metabolism," published in 1930 as one of the Plimmer series of "Monographs on Biochemistry." The author has stated in the preface that the aim of her book "has been to choose from the mass of data on the chemical activities of bacteria facts which may help us gain an insight into the essential chemical processes accompanying the life of the organisms concerned." She voices an opinion, fervently held by many, that it is time to "appraise our knowledge of bacteria as living organisms apart from their rôle as disease germs or the bearers of commercially important catalysts." Of course all of the significant fundamental knowledge of these organisms will in the end be turned to the service of man and animals. Yet it is delightful for the broadly interested bacteriologist to find such a book.

as this one written with an avowed interest in the bacteria for themselves. It is additional evidence that the time is nearly here when a refutation will be provided for Lord Balfour's statement that "though the bacteria are the subject matter of bacteriology they do not, in and for themselves, constitute its main interest." Chapters in this book deal with energy relations and fermentation, respiration, growth and nutrition, the breaking down of carbohydrates, and synthesis, the breaking down of proteins, nitrogen fixation and autotrophic bacteria. The book has the fine scientific qualities of the monographs of this series.

A great service has been rendered to "all bacteriologists in all bacteriological laboratories" by the publication in 1930 by Levine and Schoenlein of "A Compilation of Culture Media for the Cultivation of Microorganisms." In this huge book, with pages printed in double columns the formulas of about 7,000 culture mediums have been brought together, classified into groups and subgroups, and so arranged and catalogued under keys and indexes that the matter dealing with any sort of medium and the food requirements of any sort of bacterium may be found with ease. The book was prepared at the request of the Society of American Bacteriologists and financed by a grant from the Digestive Ferments Company. It is a monument to the industry of the compilers and their systematic minds. If so many kinds of culture mediums are needed by bacteria, the conclusion must be drawn that these organisms have extraordinarily fastidious food requirements. On the other hand, there is the distinct possibility that the multiplicity of minor variations of certain basic mediums is more indicative of the uncontrolled vagaries of bacteriologists than of the specialized appetites of the bacteria. Perhaps the book will serve to curb the invention of new, but unnecessary, culinary mixtures and, while providing a mine of useful information, help to stabilize the use of cultural substrates.

A small, but serviceable, companion to this compendium of culture mediums and a book with merits of its own that will appeal to the medical bacteriologist, as well as to the biochemist and industrial bacteriologist, is the "Index to the Chemical Action of Microorganisms on the Non-Nitrogenous Organic Compounds," published in 1930 by Fulmer and Werkmann. The material is so arranged that it is possible to find in this book under the name of an organism, the products produced from various substrates, under the name of the product, the organism and the substrate to be used to obtain the desired substance, and under the name of the substrate the products produced from it by various organisms. Authorities and references are cited for each statement. "Industrial Bacteriology," by Smyth and Obold, is another

book produced in 1930 showing how far the domestication of the bacteria has progressed

In an attempt to present timely summaries of the "latest results of investigations in various lines of bacteriology and immunology," Jordan and Falk, in 1928, brought out a collection of contributions from 82 authors under the title, "The Newer Knowledge of Bacteriology and Immunology." By promptness in editing and publication the book escaped the delays that cause so many textbooks to be partially out of date by the time they are issued. The knowledge in it is in many cases sufficiently new and authoritative to serve the needs of future textbooks. As may be expected from multiple authorships, the treatment of subjects is uneven, sometimes overlapping and sometimes contradictory. On the whole, I have found it a useful and stimulating book, as have others with whom I have been associated. References to various chapters in it in recently published papers indicate that as a compendium of modern knowledge in medical bacteriology and immunology it has been of general service to investigators.

Since the decline of the influence of Pettenkofer, less attention has been paid by medical bacteriologists to the relation of the soil to outbreaks of disease in man and animals. As a source of spore-bearing anaerobes, however, the soil plays a predominant rôle in the gas gangrene and tetanus of man, in botulism and in a number of other infections of man and animals. It has important connections with typhoid fever, anthrax and possibly actinomycosis. It harbors numerous micro-organisms that harmfully or beneficially affect the plants on which human beings and animals subsist. In addition, the scientific medical bacteriologist cannot afford to neglect the knowledge of bacteria gained from the study of the micro-organisms of the soil. Therefore, it is appropriate to mention in this review the "Principles of Soil Microbiology" by S. A. Waksman, published in 1927. In this compendium, chapter 30 summarizes the knowledge of the soil as a habitat for micro-organisms causing diseases of plants and animals. Recent investigations of enzymes from a micro-organism of the soil inimical to the pneumococcus indicate that this field is certain to have an even closer relationship to medical bacteriology.

If any books might be expected to exhibit the true stage of development or the degree of stability of a biologic science, these should be the volumes on classification and nomenclature of the organisms with which that science deals. In bacteriology, the chief book on taxonomy is "Beigey's Manual of Determinative Bacteriology," the third edition of which was issued in 1930. A first glance at this book gives the impression that a vast number of bacteria are classifiable, and that bacteriologists have an acceptable system of classification. But those

who have seen this book grow and change under their eyes during the past few years and those who seek to place an organism by matching its characteristics with the descriptions in Beigey's manual know that while the book reflects a moderate degree of stability in bacteriologic taxonomy, it gives evidence also of a large and shifting uncertainty in bacteriology. The manual is, in fact, a body of unofficial suggestions. Its nomenclature is not acceptable to the majority of bacteriologists, and in some cases the grouping of micro-organisms seems to violate their natural relationships. Nevertheless, the manual is an invaluable source of information. As taxonomy must change with changes in knowledge, as many descriptions of bacteria are incomplete and as most medical bacteriologists perpetuate confusion by their incorrigible laxity in taxonomic practice, a final and generally acceptable classification and nomenclature cannot be expected at this time. A recent addition to the English literature of this subject is the translation from the German of the two volumes of "Determinative Bacteriology" by Lehmann and Neumann. The translation has been made by Dr. Robert S. Breed and several associates. Since this book contains a certain amount of material on spirochetes, protozoa and fungi and on immunologic reactions, it might be placed among the handbooks of microbiology. It is appropriate, however, to review it in this paragraph dealing with the recent literature on taxonomy. Its main interest and "most permanent value," as Dr. Breed has remarked, "lies in its systematic arrangement of our knowledge regarding the still too imperfectly known and numerous types of bacteria," and in the classification and nomenclature used by Lehmann and Neumann. A distinct service has been rendered English-reading bacteriologists by making readily available this important expression of an authoritative German point of view. In addition, these volumes will serve as a valuable work of reference on the technical, biologic, taxonomic and historical matters that interest bacteriologists perennially. Finally, there is at present a renewal of the attempt to find some generally acceptable taxonomic scheme and nomenclature in bacteriology. Committees of the International Society for Microbiology and of the International Botanical Congress have been appointed to study these questions and to formulate a plan of concerted action. This book is awaited with high expectations.

The increasing knowledge of bacterial variation is apt to make the ways of most bacteriologists, especially the taxonomists, difficult for awhile. In the end, however—years hence—bacteriology will find simplifications and rationality in coordination of the completed studies of the variants and of the life cycles of the bacteria. The subject of variation in bacteria still lacks its comprehensive book. It is to be

hoped that one will be produced, gathering together all the reports of sound investigations that have been going on through many years. A great deal is already known of many phases of bacterial variability, from variations in colonies to variations in cells, from variations in metabolism virulence and toxigenicity to variations in antigenic disturbances, from such hereditary changes as those described by Mellon Lohms and Almquist, to changes that might be interpreted as evidence of the life cycles of bacteria. The accumulated mass of evidence has broken down the unbiologic convention of fixity of form and of other characteristics and restored a biologic outlook on the capacity that bacteria have in common with other living things to change in response to external and internal influences. All of these new studies are of great importance to the medical bacteriologist and epidemiologist, as they will explain more and more of the phenomena of infectious disease and elucidate some of the mysteries of epidemics. At the beginning of the period under review one of the most remarkable of the books on this subject was the "Bakterien-Cyclogenie" published in 1925 by Endeilein. In order to gain an insight into the meaning of most of the passages in this book, it is necessary for the reader to learn the large new vocabulary coined by Endeilein. It is difficult to appraise the value of his observations of sexual phases in bacterial growth through "gonits," "sperimts" and the cyclogenic stages consequent on the activities of the "mych," or ultimate nucleus, and the "mychit," or fundamental cellular unit. A great deal of new material can be found in this book. The phase of variation known as bacterial dissociation was studied exhaustively by Hadley, who begins his monograph on "Microbic Dissociation" with the statement that for the past three decades there has been accumulating an increasing mass of evidence pointing to the instability of bacterial species. After recording the results of experimental study of many of the conditions that bring about microbic dissociation, he points out that many of the important problems in modern bacteriology and pathology "have their roots in the phenomena of bacterial instability." In the course of this research, the bacteriophage was found to have such close and influential relationship to microbic dissociation that Hadley inclined to the view that both these reactions—transmissible lysis and bacterial instability—were "inseparably united in the reproductive mechanism of the bacterial cell." Bacteriophagic phenomena intensified the interest in filtrable viruses and the possibility of the existence of filtrable stages of bacteria. The latter subject has for a number of years engaged the attention of French bacteriologists. In 1929 Hauduroy summarized much of the knowledge of the filtrable forms of bacteria in his book "Les ultravirus et les formes filtrantes des microbes." More recently the

most exact account of experiments capable of demonstrating the filterable forms of bacteria is the monograph published in 1931 by Hadley and his associates, describing their work, "The Filterable Forms of Bacteria. I. A Filterable Stage in the Life History of the Shiga Dysentery Bacillus." For the first time, bacteriologists have been provided with detailed descriptions of methods and procedures for obtaining filterable stages of bacteria. This monograph is certain to stimulate much investigation in the attempt to substantiate or to disprove this most significant contention. The evidence thus far available seems to be most strongly in its favor. A more critical book dealing with morphologic variation in bacteria is Henrici's monograph, "Morphologic Variation and the Rate of Growth of Bacteria," issued in 1928. As a result of his laborious measurements of thousands of bacterial cells in various stages of growth, he found that the old monomorphic conception can no longer be considered sound, and should be modified. On the other hand, he concluded that the evidence for the existence of bacterial life cycles was inadequate to establish that conception. This field is now in a state of intense and fruitful cultivation.

The filterable viruses, during this period, have received a very large share of the interest of all and the attention of a number of skilled investigators. Their medical and economic importance is so great that it is somewhat astonishing that really intensive study of them was delayed so long. At present, however, new methods of attack from the vantage points of methods of attempted cultivation and the analysis of inclusion bodies is rapidly extending the knowledge of these minute viruses. Two comprehensive books have been published on them. The first, in 1922, was the collection of special articles under the title, "Filterable Viruses," edited by T. M. Rivers, and the second is the volume entitled "Filterable Virus and Rickettsia Diseases," by E. B. McKinley, published in 1929. Although a consideration of the rickettsiae is out of place here and really requires separate treatment in a special volume, these two books present most of the substantiated knowledge of the viruses.

So much of the research in bacteriology during this period has had its origin in the study of the phenomena of the bacteriophage that it is essential and appropriate to mention here d'Herelle's comprehensive book, "The Bacteriophage and Its Behavior," translated by G. H. Smith and published in 1926. The phenomena is so well known that a review of this book is unnecessary. The importance of the bacteriophage whatever view one may hold as to its nature, is paramount in modern studies and in conceptions of the ultimate unit of vitality, the dissociation of bacterial species and the recovery from certain acute infectious diseases.

Medical mycologists see many apparently similar forms of fungi producing different diseases and many similar diseases produced by apparently different forms of fungi. The troubles seem to lie in the variability of the fungi under different conditions and the seeming impossibility of combining systematic mycology and clinical nosology in a workable classification. Two recent books in this field clarify some of the obscurities and darken others. The first of these, essentially a medical treatise, is the collection of the Adolph Geimann lectures delivered by Castellani at the College of Medicine of the University of Illinois in 1926 and published later in book form under the title, 'Fungi and Fungous Diseases'. The book contains apparently concise descriptions of the fungi and the fungous diseases, is provided with tables for correlations and is well illustrated. It is, however, difficult for a student to establish identifications by means of this book. A broader and more "botanical" book is Henrici's "Molds, Yeasts and Actinomycetes," published in 1930, as a handbook for students of bacteriology. Most of the available knowledge of fungi is summarized in this book. It gives a valuable biologic insight into these organisms and more than fulfils the modest purposes of its author. Perhaps there are still too many uncertainties in this field to permit the publication of the sort of book for which the medical mycologist yearns.

Notable collections of the really vast accumulations of knowledge of the streptococci have been published during the past few years by D. and R. Thomson in the "Annals of the Pickett-Thomson Research Laboratory" of London. These annals are such large monographic treatments of the streptococci that they pass from the category of journals into the class of comprehensive books. In addition to presenting summaries of all the literature on the streptococci and on the relation of streptococci to scarlet fever, arthritis and rheumatic fever, the annals contain the results of photographic studies of the structure of the colony of these organisms on Crowe's medium photographed by a special apparatus using ultraviolet light. The illustrations are superb. They do not convince me, however, that they are as significant as the authors think them to be for establishing the exact relationships among the streptococci. Much additional information is required, as is usual in any determinative bacteriologic procedure.

There is a definite tendency in these days to assign the spirochetes to the general class of bacteria. Whatever their nature, the medical bacteriologist is forced by occasion and interest to concern himself with these organisms. In this case again he desires a comprehensive treatise. He has available numerous short summaries of the knowledge of the spirochetes. He will find a large store of facts in the book published by August Pettit in 1928 as a "Contribution à l'étude des

spirochetes.' One whole section of this book is given to a consideration of the jaundice-producing spirochetes—especially *Spirochaeta icterohemorrhagiae*. Other sections deal with all the types of spirochetes and the technic of studying them. The book presents the results of nearly twenty years of investigation of the spirochetes by Pettit, who began his work with Laveran in 1911.

In many of the books mentioned in this review, the authors have in one way or another, stressed the importance of veterinary medicine for human medicine. The study of pathogenic organisms should obviously include the bacteria that produce disease in animals along with those that produce disease in man. The liaison, however, has not always been as close as it should be. In deploiring this fact, Topley and Willson write: "In no branch of medical science is the sterilizing effect of the anthropocentric attitude more obvious than in the study of bacterial infection." This implies that almost too much study by man has been devoted to the infections of mankind. A closer relationship between human and veterinary medicine is being voluntarily sought by the intelligent medical bacteriologists and forced by the episodes of undulant fever, tularemia and a number of diseases common to man and animals. The most recent correlative book on this subject is the small volume, "Diseases Transmitted from Animals to Man," published by T. G. Hull in 1930. It is a useful book as far as it goes, and is good enough to stimulate the wish that the author would enlarge it in the next edition.

It has been necessary to omit from this review the mention of many books, both foreign and American. Enough has been written, however, to record the extraordinary activity in bacteriology that has been characteristic of the past five years. If there has been no end of making many books, this has been due to the limitless material from which to make them.

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Paleopathologic Report

OSTEITIS FIBROSA IN A SKELETON OF A PREHISTORIC AMERICAN INDIAN^{*}

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In an attempt to understand prehistoric American Indian life one must consider not only the cultural aspects such as artifacts and type of burial, but also the pathologic conditions encountered. Anomalous or pathologic conditions are in themselves sufficient to modify the existence of an individual. An unusual example of a pathologic condition was excavated by the University of Chicago Archaeological Survey, from mound F14, Fulton County, Lewistown, Ill. during the summer session of 1930.

The skeleton is that of a man approximately 35 years old. He was a cripple with an affliction involving practically the entire left side of the body. During life the left leg was bent over the right at about the level of the knee. The left foot and toes were markedly extended and permanently fixed. The right leg curved toward the median line. Walking must have been difficult, if not almost impossible, as even the pelvic and body axes were obliquely aligned. The left half of the face was askew. A more or less constant rheumatic type of pain must have played no small part in his existence. Yet with this man there were found many distinctive artifacts, such as bear's teeth, bone needles, a shell necklace, discoids and an effigy pipe. All these factors indicate that he probably held some important position among his fellows, and it becomes more significant when one considers the paucity of material expression associated with other burials in the same mound¹. He may even have been the traditional "medicine man."

The exact chronological position of this skeleton is necessarily a matter of estimation. The mound in which it was found belongs to the last of the three bluff cultures which precedes the Columbian era by several centuries, and is subsequent to the Hopewell culture (about 2,000 years old). Thus, its age may safely be approximated at 1,000 years.

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1 The apotheosis of cripples is by no means a new idea. Well known examples of this are the deification of achondroplastic dwarfs by the Egyptians as described by Rufer, Sir M. Armand. *Studies in the Paleopathology of Egypt* ed. by R. L. Moodie, Chicago University of Chicago Press 1921, pp. 35-49. Dawson W. R. *Dwarfs and Hunchbacks in Ancient Egypt* Ann. M. Hist. 9 315 1927.

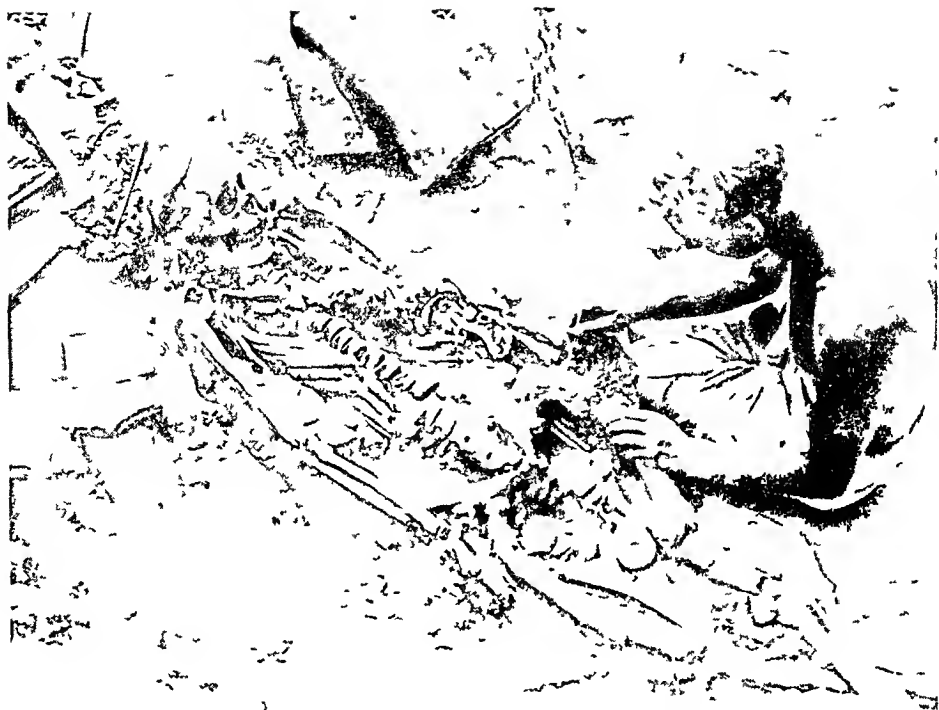


Fig 1—View in situ of skeleton (F 14-50) showing osteitis fibrosa, Mr George Neumann removing the left femur (see fig 2) The number 51 refers to a skeleton the skull of which lay directly beneath the fragile pelvis of this specimen and was responsible for considerable damage Note coxa vara position of left leg



Fig 2—Posterior view of the left femur, and posterolateral view of the right

A study of the skeleton indicates that the man to whom it belonged was afflicted with osteitis fibrosa as evidenced by the following observations²

The left femur presents the most striking pathologic changes in the upper third of the bone. These changes consist of a marked medial bending and an extensive enlargement and overgrowth of bone, with evidence of cavity formation. The bending of the head and neck of the femur on its shaft is such that the axes of these form an angle of approximately 45 degrees downward and is probably not due to previous fracture. This must have required the man to hold the leg in a marked position of coxa vara crossing in front of the right leg at about the level of the knee. The enlarged portion of the femur begins slightly above the junction of the upper and middle third of the shaft. Here there is a bony overhanging crest. The anterior surface of this swelling is relatively smooth and presents few perforations or porosities. Those present are mainly at either end of the enlargement. The perforations appearing on the lateral surface seem to have been made during the work of excavation. Bony trabeculations and perforations make up the posterior surface of this region of the femur and in the upper part bony cords radiate from the margin of the femoral head to the trochanter. The lower portion of the posterior surface presents many projecting osteophytic growths.

The interior of the enlarged portion forms a cyst or large cavity. In its upper portion the cavity is filled with soft fine, irregular, sponge-like bone, derived from the pathologic changes in the bone marrow. The cortical bone about these cavities is very fragile and in places exceedingly thin. A lacelike trabeculation associated with spongy bone is found to extend through the entire marrow cavity on the lateral side. Just above the lateral condyle on the popliteal surface is an eroded, perforated, ulcer-like area, connecting with the peculiar bone formation described in the marrow cavity. This appears to be an early stage in the peripheral invasion of the disease.

In the right femur the pathologic changes are found in the proximal fourth of the bone, and are by no means so extensive. The normal contours are increased in size, with a nodular enlargement above the intertrochanteric crest. The surface here is perforated by hiatus from

2 As here considered, osteitis fibrosa is a primary disease in contrast with the secondary fibrous osteitis often definitely associated with inflammatory lesions. Primary osteitis fibrosa "is a distinct clinical entity is very liable to be confounded with osteomalacia osteitis deformans or with central bone tumors, and is very puzzling to the practitioner," according to R. L. Knaggs (*The Inflammatory and Toxic Diseases of Bone* New York: William Wood & Company, 1926, p. 1246) and I may add that our position as paleopathologists diagnosing only from the osseous remains is at times no less dilemmatic.

4 to 8 mm in diameter, leading into a cavity, continuous with that of the bone marrow. Spongy bone is also found in this cavity. In the unaffected portions the cortex of both femurs is of normal thickness.

The right tibia exhibits a diffuse nodular swelling slightly above the middle of the shaft. On the medial surface there are two deeply eroded areas in the cortex, the smaller of which (2 by 4 cm) is surrounded by a slightly raised, eburnated ring of bone. Its base is composed of soft spongy bone and irregular bony trabeculae around numerous hiatus which lead into the marrow cavity. The larger eroded area (3 by 7 cm) is similar in appearance except that the margin is eburnated only in the back and here blends with a diffuse nodulation on the posterior surface. The left tibia was badly broken in situ by roots and only the lower third of the shaft shows nodular enlargements.

The fibulae of both the right and the left legs present all the pathologic changes described. There are nodules associated with eroded



Fig. 3—Roentgenogram of the left femur showing cyst formation, thinning of cortical bone, trabeculation and abnormal deposition of bone.

areas, and cavities indicative of either cysts or fibrous areas, in various portions of the shaft. Such regions contain spongy bone and trabeculae and have a rarefied cortex. It may be noted here that in the long bones none of the articular surfaces are involved.

The bones of the right foot appear to be unaffected, while those of the left foot show a general increase in porosity of surface. Only the first and second metatarsals of the left foot show any significant pathologic changes. The first metatarsal contains spongy bone throughout and an eroded perforation on the distal end of the dorsal surface. The second metatarsal shows only an eroded area at the proximal end. As the bones of the left foot were uncovered in situ, they delineated the position of a marked talipes equinus.

In the right os coxae only the ischiopubic ramus and ischial tuberosity are involved by a single cystic swelling extending from the center of the tuberosity into the ramus. The erosion of the surface in this region extends upward to the posterior surface of the acetabular portion



Fig 4—Medial views of right and left humeri and of right tibia



Fig 5—Lateral aspect of left os coxae and posterior view of sacrum. The loss of osseous material in the lower portion of the ileum and that in the right side of the sacrum are due to crushing in the grave and do not represent a pathologic condition. However, the extensive involvement of the bones is evident. The first coccygeal segment has ankylosed with the sacrum.

of the ilium. A small osteophyte is present at the attachment of the transverse ligament to the acetabular margin. The left os coxæ had been crushed in the grave, but sufficient material remains to show the extensive pathologic changes that had taken place. The portion of the ilium above the acetabulum is ballooned out with a series of cavities to a width of 6.5 cm. The lateral and medial surfaces are much eroded, and many of the hiatus show eburnated margins. The interiors of the cavities contain trabeculations and spongy bone. The sacral articular surface is missing.

Sacral involvement is primarily on the left side, as in the pelvis. The enlargement is directed laterally, so that the anterior sacral foramina become ellipses. These open into a large cavity between the first and fifth sacral vertebrae, continuous with the posterior foraminae and with the sacral canal. The articular surface of the left side is much eroded, jagged and perforated, indicating that this joint formed no barrier to the extension of the disease process. A bending of the lower portion of the sacrum to the right may be due to long continued pathologic action.

Extensive changes are to be found in some of the ribs. The first left rib is about three times the size of its opposite in width and breadth but its length is not increased. Its surface is somewhat eroded at the head and the body is a mere cavity with thin cortical bony walls. The second, third, fourth and tenth ribs are unaffected. Of the remaining ribs of the left side it was possible to save only the seventh, ninth and eleventh. These are merely fragile laceworks of bone with only the heads retaining their identity. As their condition is irreparable, one must rely on the accompanying illustrations. On the right side the ribs are unaffected, except for a small portion on the anterior surface at the angle of the fifth.

In the vertebrae the pathologic changes are similar to those described in the other bones. The seventh cervical vertebra has cavitous transverse processes and spine, with characteristic erosion and perforations of the surface. Like changes are also found on the left transverse processes of the fifth to the tenth thoracic vertebrae, and the ninth, tenth and eleventh show involvement of the right transverse processes. The body of the eighth thoracic and that of the second lumbar vertebrae have been perforated by the pathologic process. An incipient perforation is seen in the body of the sixth thoracic vertebra.

The involvement of the skull by the disease is limited to contiguous portions of the left maxilla, palatine bone and pterygoid process of the sphenoid. The anterior portion of the palate is also affected causing a dissymmetry of the nasal aperture on the left side. The palate here is 1.5 cm thick but is of normal size posteriorly. It bulges some-



Fig 6—Vertebral column viewed from the left side, the third lumbar vertebra was broken, a space representing its location At the right are the first, second, third, seventh, ninth and eleventh ribs of the left side, of which the second and third are normal



Fig 7—Roentgenogram of ribs, showing extensive cyst formation and rarefaction

what below the normal palatal plate and presents an eroded surface. The pterygoid region on the left side is composed of a hard, porous enlargement of bone with only narrow ridges suggesting the pterygoid laminae. The base of the normal right pterygoid process measures 1.2 cm. across, while the base of the affected side measures 2.5 cm., the pterygoid fossa being essentially eliminated. The palatine canal and other foraminae in this region are patent.

The foregoing material appears to me to indicate clearly that here for the first time is a case of osteitis fibrosa in a prehistoric American skeleton. Osteitis deformans has been encountered, but differs from osteitis fibrosa in important features, both in its effect on the living person and in the condition of the bones after death.³

Osteitis fibrosa is a multiple disease of bone characterized by resorption of bone and its replacement by a fibrous connective tissue, associated with formation of cysts. The disease very seldom appears after the age of 40 and may occur before puberty. In recent years many cases have been found in association with parathyroid adenoma. The pathologic changes in the bones show (1) extensive resorption of bone, which I have termed, macroscopically, erosion, (2) irregular, malformed deposition of bone throughout the fibrous growth,⁴ (3) formation of cavities associated with swelling beyond the normal contours of the bone, (4) rarefaction of cortical bone in the involved regions only, the cortical bone elsewhere being of normal thickness and consistency, and (5) a characteristic nodular appearance, as the disease possesses no uniformity of distribution or progress.

Roentgenograms of the entire skeleton have been made, and those of the bones described in detail substantiate the pathologic changes enumerated in foregoing paragraphs.⁵ The left femur and ribs present the most characteristic features of the disease (see figs 3 and 7).

3 There is a recent tendency to consider osteitis fibrosa, osteitis deformans and osteomalacia as a clinical group under the term of osteodystrophia fibrosa. However, from a paleopathologic point of view it seems advisable to retain them as entities so that any remains of a doubtful pathologic nature may be more critically approached, and thus rescued from the oblivion imposed by an all inclusive term.

4 It is understood that the replacement of bone by fibrous tissue can be seen only in fresh specimens, and it is during this active stage of the disease when fibrous tissue predominates, that the bending occurs.

5 Some of the bones that appear normal grossly show in the roentgenograms small areas of rarefaction, which may indicate an incipient process of the disease, but which are indistinguishable from the condition known as spotted atrophy. Such areas are found in the right calcaneus, the right and left astragalus, several of the ribs on the right side and the bodies of the sixth, eighth and ninth thoracic and the second lumbar vertebrae. The acetabula, the heads of the femurs and a few of the vertebral bodies show minute osteo-arthritic changes which are negligible.

Involvement of the skull in the specimen is limited to the left side of the base as described, the roentgenograms showing nothing typical of the condition, the calvarium being normal in thickness and exhibiting no rarefaction

Osteitis deformans, on the other hand, differs in the following characteristics 1 As the bone marrow is transformed into fibrous tissue and ultimately into bone, it encroaches on the inner surface of the cortex increasing its thickness 2 A similar change takes place on the outside through the subperiosteal deposition of layers of bone Thus in osteitis deformans the cortex may become 1 cm or more in thickness, which characteristically is uniform throughout the length of the bone, and is seldom associated with the formation of cysts In typical cases the thickness of the calvarium is increased four or more times the normal Further, osteitis deformans is a disease of middle age, rarely beginning before the age of 40 These characteristics obviously do not obtain in the specimen described

It is noteworthy that this case may be classed among the rarities because the involvement is so extensive, although practically unilateral

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6 Since the foregoing observations were submitted for publication two prehistoric skeletons showing pathologic changes have been reported, for which the diagnosis of osteitis fibrosa has been suggested The first, showing a bilateral involvement of the humeri only, was described by Leon Pales in his recent book, "Paleopathologie et pathologie comparative," published in Paris by Masson & Cie, 1930 The second is reported by E A Hooton, as follows "Catalogue no 60061, sex doubtful, aged 35-39 Diagnosis, (1) Spondylitis deformans, (2) Periostitis of mid shaft of left tibia H U Williams, 'probably osteitis fibrosa,'" The Indians of the Pecos Pueblo A Study of Their Skeletal Remains, New Haven, Yale University Press, 1930

Notes and News

University News, Appointments, Promotion, Resignations, etc—Simon Fleener, director of the Rockefeller Institute for Medical Research, has been elected a corresponding member of the French Academy of Sciences in the section of medicine and surgery

James Lorraine Smith, professor of pathology and dean of the faculty of medicine at the University of Edinburgh, died on April 18, 1931

The order of the White Lion has been conferred on Frederick G. Novy, professor of bacteriology in the University of Michigan, by the president of the Republic of Czechoslovakia

James R. Cash, professor of pathology in Peiping Union Medical College has been appointed professor and head of the department of pathology in the school of medicine of the University of Virginia

Richard V. Lamar, professor of pathology and bacteriology in the school of medicine of the University of Georgia, has resigned to accept the position of pathologist in the state hospital at Nulledgeville

It is reported John A. Kolmer has been appointed professor of immunology and chemotherapy in the Temple University school of medicine, Philadelphia

Israel Davidsohn, formerly pathologist to the Mount Sinai Hospital in Philadelphia, has assumed the duties of pathologist to the Mount Sinai Hospital in Chicago

Society News—At its recent meeting the American Association for Cancer Research elected Francis Carter Wood president, Edward B. Krumbhaar vice-president and William H. Woglom secretary and treasurer

The following are the officers of the American Society of Experimental Pathology for the year 1931-1932: president, Samuel R. Haythorn, vice-president, Peyton Rous, secretary-treasurer, C. Phillip Miller, Jr., councillors, Carl V. Weller and S. Bert Wolbach

At the annual meeting of the American Association of Pathologists and Bacteriologists in Cleveland, Ward J. MacNeal was elected president, E. T. Bell vice-president, G. B. Mallory treasurer, Howard T. Karsner secretary and O. T. Avery councillor. The next annual meeting of this society will be held in Philadelphia on March 24 and 25, 1932

Deaths—Aldred Scott Warthin, Professor of Pathology in the University of Michigan since 1903, died on May 23, at the age of 65 years

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

JAUNDICE IN EXPERIMENTAL COCCIDIOSIS OF RABBITS GEORGE W BACHMAN and PARIS E MENENDEZ, Am J Hyg **12** 650, 1930

Tests on 31 rabbits infected with *Emmeia stiedae* gave 111 positive reactions for bilirubin, of which 90.1 per cent were direct, 8.1 per cent indirect and 1.8 per cent were biphasic. One rabbit slightly infected failed to give a positive reaction. The large variations in quantitative estimates of bilirubin contents in these rabbits are probably due in part to the fact that the determinations were made at intervals of days and not at intervals of hours and also to the amount of epithelial destruction of the bile ducts during the various stages of schizogony. No attempt was made to explain the indirect and biphasic reactions obtained in these tests. The intensity of the infection found in some of these rabbits could have caused the rupture of small blood vessels and the destruction of hepatic cells, which would be sufficient to account for the small percentage of hemolytic jaundice. The high percentage of direct immediate reactions obtained in these tests indicates obstructive jaundice. Microscopic studies of stained sections of livers in the early stages of schizogony show the epithelial cells of biliary passages parasitized and swollen. In the latter stages of the infection the biliary passages may be seen plugged with proliferated cells of the epithelium and oocysts. In heavy infections the gall ducts and gallbladder are plugged with the numerous orange-yellow colored oocysts. The compaction of these oocysts gives rise to obstructive jaundice.

AUTHORS' SUMMARY

EDEMA HERMAN ELWIN, Am J M Sc **180** 781, 1930

We have thus come to the understanding that in every case of general edema there is a slowing up in the rate of movement of water from the depots through the tissue barriers to the blood stream. With the normal intake of water and salt and their rapid removal from the blood into the tissues, the free water there is rapidly increased. When a certain amount of water has accumulated, it becomes visible as edema. The slowing is the result of a central regulatory change and affects the constellation of electrolytes in the tissue barriers through which the water moves to the blood and lymph streams. This slowing is produced, first, whenever the water content of the blood threatens to be unduly increased, as in cardiac failure, or in acute diffuse nephritis, second, when the change is primarily in the regulatory center, along with the depression of other vegetative functions, especially of the basal metabolic rate. This is the case in chronic undernutrition and in chronic wasting disease. Third, it is produced when there is a primary disturbance in the central regulation for the control of sodium chloride in the body. This is so in certain cases of edema without cardiac or renal diseases, and without chronic undernutrition.

AUTHOR'S SUMMARY

OVARIAN AND PITUITARY CHANGES ASSOCIATED WITH HYDATIDIFORM MOLE AND CHORIO-EPITHELIOMA E NOVAK and A K KOIF, Am J Obst & Gynec **20** 481, 1930

According to certain observers, multiple lutein cysts of the ovaries occur in association with hydatidiform mole in 60 per cent of cases and with chorio-epithelioma in about 10 per cent. Most of the statements are based on the results of abdominal

palpation. Such cysts disappear spontaneously after evacuation of the uterus. The authors had occasion to examine the uterine contents and ovaries of four women, two of whom had a hydatidiform mole, the other two a chorio-epithelioma. The pituitary gland of one of the latter was also available for study. The ovaries of all the women contained cysts—the "hyperreactio lutealis polycystica." In the pituitary, only the usual changes accompanying pregnancy existed, but these had persisted longer than usual. To explain the conditions the following inter-reactions are assumed. The trophoblastic increase in chorio-epithelioma (persisting in the metastases after evacuation of the uterus) is responsible for the pituitary reaction. The anterior lobe of the pituitary, "the motor of the ovary" in its normal cyclical activity also causes the ovarian changes of normal pregnancy and also those occurring in hydatidiform mole and chorio-epithelioma.

GEORGE RUKSTINAT

A COMPARISON BETWEEN SIMULTANEOUS EQUAL-SIZED, CLOSED OBSTRUCTION OF THE DUODENUM AND ILEUM J J MORION and W C SULLIVAN, Arch Surg **21** 531, 1930

The distal 10 cm of the ileum and of the duodenum were obstructed in dogs. Every twenty-four hours the loops were aspirated, and the contents measured and reprojected in order to estimate accurately the rate of secretion without disturbing the intra-intestinal pressure relations which had occurred. The secretory rate for the ileum is practically negligible as compared with that of the duodenum, which is rapid. The intra-enteric pressure is from four to seven times higher in twenty-four hours in the duodenum than in the ileum. The distensibility of both loops is about the same, but the ileum increases in length as compared with the obstructed loop of the duodenum. In those cases in which spontaneous rupture occurred in the closed loops, the closed duodenal loop was the one affected. Death in these animals was due to peritonitis. In the other animals, death was due to toxemia, and after death it was noted that a pressure equal to 1,600 mm of mercury was necessary to rupture the closed loops. However, as rigor mortis advances, the pressure required to produce rupture is lower. This is due to the loss of elasticity of the musculature.

N ENZER

THE EFFECT OF PERICARDIOTOMY ON THE MECHANICS OF THE CIRCULATION C S BECK and W V COX, Arch Surg **21** 1023, 1930

Experiments were made on dogs to determine the influence of atmospheric pressure on the action of the heart after pericardiostomy. A preliminary operation is necessary in dogs, because there is no triangle of safety in the precordial zone. Hence, the pericardium must be sutured to the left thoracic wall over an area about 3 cm in diameter. Pericardiostomy may be performed about seven weeks later, and arterial and venous pressure and cardiac output determined. Following pericardiostomy, there is a sustained rise in venous pressure and a fall in the arterial pressure of from 8 to 30 mm of mercury. Atmospheric pressure acts as an air tamponade on the heart and the great vessels within the pericardial sac, and produces dilatation of the sac. Hence, operative procedures can hold out reasonable hope for success only in cases with adequate circulation.

N ENZER

A NEW TRANSMISSIBLE STRAIN OF THE LEUCOSIS (LEUCEMIA) OF FOWLS J FURTH, J Exper Med **53** 243, 1931

Myeloid leucosis and erythroleukosis can be transmitted from one bird to others by emulsions of infiltrated organs, whole blood cells and plasma. Inoculation is more often successful with blood cells or with whole blood than with plasma or with emulsions of organs infiltrated as the result of leucosis. Inoculation with material from a bird with myeloid leucosis or with erythroleukosis produces both conditions and in many instances mixed forms with characteristics of both. Evi-

dence is wanting that lymphoid leukosis is caused by the agent that transmits myeloid leukosis and erythro-leukosis. The occurrence of lymphoid leukosis among the birds inoculated with material from myeloid leukosis or erythro-leukosis may be explained as spontaneous disease. Injury to cellular structure by treatment with distilled water or by repeated freezing and thawing does not destroy the agent that transmits the disease. Berkefeld filtrates have failed to transmit regularly myeloid leukoses or erythro-leukosis. The evidence obtained shows, however, that the transmissible agent is filterable, although there are technical difficulties in its filtration.

AUTHOR'S SUMMARY

TRANSMISSION EXPERIMENTS WITH LEUCOSIS OF FOWLS E. L. STUBBS and J. FURTH, *J. Exper. Med.* **53** 269, 1931

It is shown, in a carefully controlled experiment that the leukemia of fowls can be readily transmitted from chicken to chicken by injection. Of twenty-five fowls, thirteen were given intravenous injections of blood from a chicken with erythro-leukosis and twelve injections of blood from a chicken with myeloid leukosis. The birds that received the injections and an equal number of controls that did not were kept in tiers of alternating cages under as nearly identical conditions as possible. The donors, the controls and the birds that were given injections were all of the same stock and of the same age. In the two series, thirteen or 52 per cent of the twenty-five fowls that were inoculated developed leukemia within from four to ten weeks after injection. The two types of leukemia, erythro-leukosis and myeloid leukosis, developed in both groups irrespective of the type used for injection. Among controls that were not given injections, erythro-leukosis or myeloid leukosis were not observed. Lymphoid leukosis occurred in one fowl that had received an injection but since it also occurred in one control it may be assumed that it was probably not caused by the material used for injection.

AUTHORS' SUMMARY

A CRITERION OF HEMORRHAGIC DIATHESIS IN EXPERIMENTAL SCURVY G. DALLDORF, *J. Exper. Med.* **53** 289, 1931

The degree of scorbutic change in the vessels of animals with experimental scurvy can be roughly measured by establishing the amount of negative pressure required to produce petechial hemorrhages in the skin. The test shows that the hemorrhagic diathesis in experimental scurvy develops earlier than any other known sign of the disease and that it persists in some degree throughout. The response of the blood vessels to the administration of antiscorbutic substances is extremely rapid as shown by the test, but it varies with the amount of antiscorbutic substance given and its method of administration. The changes in the resistance of the vessels follows a curve which rises toward recovery during the end of the first week that a scorbutic diet is fed, reaches a peak in the second week, and then falls steadily during the remainder of the course of the disease. This indicates that the course of the disease is not constant and progressive. The test may have clinical value in the diagnosis of scurvy.

AUTHOR'S SUMMARY

EXPERIMENTAL DUST INHALATION IN GUINEA PIGS F. HAYNES, *J. Hyg.* **31** 96, 1931

All inhaled particles are rapidly ingested by certain individual cells belonging to the alveolar epithelium. These cells (dust cells or phagocytes) remain in the parenchyma of the lung until they have ingested an amount of dust constituting the cell's saturation load. This load varies with different dusts. A cell that has attained its saturation load sooner or later becomes detached from the alveolar wall and either migrates into the lymphatics or becomes free in the alveolus. In the former case, it passes into the pulmonary lymphoid tissue and thence to the

bronchial lymph glands. In the latter case, it passes up the bronchial tree to be either coughed out or swallowed. Dust cells that speedily leave the alveolar wall are principally eliminated by the bronchi. In the case of a dust cell being eliminated from the lung via the lymphatics, it may be arrested in the periatrial lymphatics on account of its bulk. The dam thus produced offers obstruction to the passage of other dust cells shed into the alveoli. Groups of free dust cells in the obstructed alveoli form plaques, which degenerate and liberate their dust. This is again ingested, and the irritation caused by such a process may lead to fibrosis. The continued presence of dust-laden cells in the lymphatics may set up a foreign body irritation, with resulting fibrosis. Most inhaled particles contain soluble matter, at least to a very small extent. The solute may be either harmlessly active or toxic. If the former, the cell is stimulated to detach itself from the alveolar wall, and so remove the dust. If the latter, the solute effects the viability of the phagocyte, which becomes less able to detach itself. At the same time the solute diffuses into the adjacent tissues, with irritation to them, and consequent fibrosis. The more soluble form of a substance causes greater pulmonary damage than the less soluble. The solute, therefore, plays a large part in the determination of damage.

While many dusts cause pulmonary fibrosis, silica is the dust par excellence predisposing to tuberculosis. This is doubtless due to its influence in forming a medium suitable not only for the survival but the proliferation of the tubercle bacillus in the lung (Kettle, private communication). The harmful effects of soluble silica may be neutralized by simultaneous administration of basic dusts such as aluminum hydroxide or magnesium carbonate, though the latter are themselves harmful when inhaled alone. It is suggested that their respective solutes combine to form monosilicate. Monosilicates do not appear to have any harmful effect on the lung. Heavy inhalations of any dust are liable to cause pulmonary damage. The intensity of the initial pulmonary reaction to a dust is very generally in inverse ratio to the degree of eventual damage caused by the dust.

AUTHOR'S SUMMARY

THE EFFECTS OF INHALATION OF BENZINE AND BENZENE. M. SCHMIDTMANN, *Klin Wchnschr* 9 2106, 1930

The inhalation of small quantities of benzine and benzene over long periods gave rise in animals to chronic bronchitis, emphysema, epithelial proliferation in bronchi and alveoli and atelectasis, but carcinoma did not develop. The anemia and other blood changes characteristic of benzene poisoning gradually appeared.

GOUT IN AN INFANT FIVE WEEKS OF AGE. E. MAYR V. SCHOPF, *Klin Wchnschr* 9 2148, 1930

The author reports the details of the clinical course and examinations of the tissue in a case of gout in a child 5 weeks old. The urates were formed from endogenous purines. The kidneys were contracted.

EDWIN F. HIRSCH

HYPERTENSIVISM WITH HYPOGLYCEMIC SYMPTOMS. F. KRAUSE, *Klin Wchnschr* 9 2346, 1930

A disease was observed in a man, aged 43, which was caused by hypoglycemia, and which is interpreted as a hypoglycemic reaction of the organism. This condition of spontaneous hypoglycemia is caused by hypersecretion of insulin, and the morphologic basis is probably a tumor of the pancreas.

AUTHOR'S SUMMARY

CIRCULATORY AND TUBULAR INSUFFICIENCIES OF THE KIDNEY. ERWIN BECHER, *Klin Wchnschr* 9 2350, 1930

Circulatory and tubular insufficiencies of the kidney are distinguishable. In the circulatory insufficiency which occurs with acute nephritis and cardiac insuffi-

ciency, the total nonprotein nitrogen of the blood, the urea and the uric acid are increased, and other changes are absent. This is due to the decreased circulation of the blood through the kidney and without, or only slightly, altered tubular function. With true tubular insufficiency, there is a marked increase of the putrefactive substances of the blood as well as of the nitrogenous substances. There are a hyposthenuria or isosthenuria and light-colored urine, because the oxidation of the urochrome in the kidney does not occur.

AUTHOR'S SUMMARY

BLOOD DEPRESSOR SUBSTANCE IN TISSUES FRITZ LANGE, München med Wchnschr **77** 2095, 1930

A thermostable substance with depressor properties has been extracted from many different visceral tissues, and by exclusion is thought to be held in the peripheral portions of small blood vessels. Renal tissues contain an appreciable amount of this substance. The ingestion of renal tissue has been found in cats and man to lower the blood pressure. Preliminary tests indicate that the active substance is not purine, choline or histamine.

EDWIN F. HIRSCH

THE INFLUENCE OF THE SYMPATHETIC NERVOUS SYSTEM ON THE PANCREAS BORIS GOLDSTEIN, Ztschr f d ges exper Med **74** 128, 1930

Experiments on the isolated pancreas indicate that the effect of the sympathetic nervous system on the secretory activity of the pancreas is exerted in two ways: it strengthens the ferment-forming processes and it helps to retain the ferments in the cells (apparently by affecting the cellular permeability).

PEARL ZEEK

Pathologic Anatomy

STRUCTURAL CHANGES IN YELLOW FEVER O. KLOTZ and T. H. BELT, Am J Path **6** 655, 663 and 689, 1930

In yellow fever, the spleen, like the liver, presents no distinctive gross features comparable with those seen under the microscope. Active hyperemia is met with in about 80 per cent of cases, but is unaccompanied by leukocytic infiltration. There is absence of hyperplasia in the fixed tissues of the pulp. Changes in the malpighian corpuscles characterize the splenic picture. Here we recognize four phases of the reaction:

- 1 Mononucleosis. The type cell is an undifferentiated mononuclear derived from the reticular tissue of the follicle, it never entirely disappears during the entire course of the disease.

- 2 Lymphopenia. There is a striking loss of lymphocytes from the whole organ, which persists throughout the reaction.

- 3 Hyperplasia of the fixed tissues of the follicle. False germinal centers are formed.

- 4 Degeneration. This is manifested throughout the whole spleen by vesicular nuclei and waxy degeneration of cytoplasm. False germinal centers undergo retrograde changes, amounting sometimes to actual necrosis. Pseudomitosis of the primitive mononuclears is observed. Large fragmented nuclear forms appear in the pulp.

A third of the cases show a few large multinucleate giant cells resembling megakaryocytes. A moderate eosinophilia is commonly observed in the later stages of the reaction. Changes in lymph glands parallel those in the splenic corpuscles, which is evidence of the fact that the toxin of yellow fever has a selective action on lymphopoietic tissue. We have found a careful examination of the spleen to be

frequently helpful in facilitating a pathologic diagnosis when yellow fever must be differentiated from other conditions giving rise to lesions in the liver and kidneys

Grossly, the liver in yellow fever is characterized by the absence of distinctive changes such as are seen under the microscope. Microscopically, the hepatic tissue presents noninflammatory necrosis and necrobiosis of the parenchyma, unaccompanied by collapse of the tissue or interstitial hemorrhage. The outstanding change is a coagulative hyaline necrosis (the Councilman lesion), which does not attack the hepatic cells in an orderly fashion, but occurs as a diffusely sprinkled lesion often most marked in the midzone (the da Rocha Lima distribution). This specific necrosis is always preceded or accompanied by fatty degeneration and cloudy swelling. In the earliest stages it is characterized by the formation of dense acidophil masses within the neutrophil cytoplasm of the hepatic cells. Later, discrete, highly refractile, hyaline globular bodies appear, often possessing a flattened, pyknotic nucleus at the periphery of the mass. These bodies are usually honeycombed with fat vacuoles which they have incorporated. The process goes on to massive involvement of parenchymal tissue and ends in cellular disintegration, but no appreciable autolysis of the affected cell structures is seen in the acute stages. The Kupffer cells suffer some damage, but not necrosis. The vascular system, biliary channels and stroma are uninvolved in the disease. Specific nuclear inclusions were found in the livers of seventeen of nineteen monkeys of the species *Macacus rhesus*, and in those of twenty-three of ninety-three human beings with yellow fever. Their identification was attended with difficulties, but when their presence could be established the diagnosis was thereby facilitated. The store of glycogen in the liver is depleted in proportion to the severity of the lesion. The lesions of the liver in yellow fever possess several features in common with the lesions of the liver in other diseases due to virus.

Six *rhesus* monkeys which had recovered from experimental yellow fever showed complete and scarless regeneration of the liver and kidney. This bears out clinical evidence that neither cirrhosis of the liver nor contracted kidney follows yellow fever in man. Special attention is directed to the sequence of events taking place in the liver. Except in cases of chloroform poisoning, hepatic damage of equal magnitude rarely occurs without producing some scar formation. The liver in yellow fever proves that destruction of parenchymal cells alone is not a sufficient stimulus to induce replacement fibrosis. The absence of fibrosis in the liver and kidney is due to a peculiar immunity which the stromal structures manifest toward yellow fever; there is no stimulation of connective tissue elements during the acute stage of the disease. The reasons for this are, we believe, related to the noninflammatory, nonautolytic character of the acute pathologic process and to the absence of thrombosis in the small parenchymal blood vessels. Regeneration originates in islands of parenchymal cells that have survived the attack, and quickly restores the tissues to their original state.

AUTHORS' SUMMARIES

ENDOCARDIAL POCKETS OTTO SAPHIR, Am J Path 6 733, 1930

In two cases of subacute bacterial endocarditis of the aortic and mitral valves with insufficiency of the aortic valve, endocardial pockets with openings toward the aorta were found on the interventricular septum of the left ventricle. The initial lesion which brought about the formation of the pockets was a circumscribed parietal endocarditis. The continuous regurgitation formed the pockets secondarily. In one case of rheumatic endocarditis of the mitral valve with insufficiency of this valve, endocardial pockets were present in the left auricle. These pockets were open toward the mitral valve. They also were inflammatory in origin and were formed secondarily by the regurgitation after the insufficiency of the mitral valve had been established. In two cases of syphilitic involvement of the aortic valve with insufficiency of this valve, endocardial pockets opening toward the aorta were found. These pockets were caused primarily by the mechanical irritation of the regurgitating blood columns. Two cases of syphilitic involvement of the aortic valve with insufficiency of this valve and marked stenosis

of the conus arteriosus sinister, and one case of rheumatic endocarditis of the aortic valve with stenosis of its orifice, showed endocardial pockets on the interventricular surface of the left ventricle. These pockets were open toward the apex of the heart. They were brought about by the mechanical irritation of the systolic blood stream acting as a trauma on the endocardium in the region of the stenosed portions. Diastolic endocardial pockets are evidence in favor of the view of actual regurgitation of blood volume. The nomenclature of "diastolic pockets," referring to those open toward the aorta, and "systolic pockets," referring to those open toward the apex (Krasso), is justified. Endocardial pockets cannot be regarded as manifestations of functional adaptation.

AUTHOR'S SUMMARY

TRANSFORMATION OF SINUSOIDAL ENDOTHELIUM INTO THE ORDINARY CAPILLARY TYPE F A McJUNKIN, *Am J Path* 7 9, 1931

In granulation tissue within the liver, the capillaries may arise in the usual way by angioblastic proliferation, or sinusoids may persist as capillaries. In both instances the vessels are continuous with the sinusoids in the adjoining lobules. With loss of contact with living hepatic epithelium the endothelium becomes less phagocytic. The peculiarities of sinusoidal endothelium depend on its functional activity, which, in turn, is determined by its normal histologic position. From the behavior of sinusoidal endothelium present in granulation tissue, it appears not to be a distinctive type of cell.

AUTHOR'S SUMMARY

THE CIRCULATORY PATTERN IN THE ISLANDS OF LANGERHANS J S P BECK and B N BERG, *Am J Path* 7 31, 1931

An anatomic study of the circulatory pattern in the islands of Langerhans was made. The arrangement corresponded with observations made in vivo. The importance of the anatomic arrangement of the blood supply in preserving the islands in the presence of circulatory disturbances in the pancreas is discussed.

AUTHORS' SUMMARY

INTERACINAR EPITHELIUM OF THE THYROID GLAND A R MORITZ, *Am J Path* 7 37, 1931

This study indicates that in normal thyroid glands of fetuses, children and adults, in pathologic glands the seat of hypertrophy and hyperplasia, in nodular goiter and in adenomas of the thyroid gland, the mechanics of hyperplasia are essentially similar. New follicles are formed by intrafollicular and extrafollicular proliferation of epithelium, and the secondary follicles may lose their parent connection and become isolated units. In the scattered foci of hyperplasia in normal thyroid glands, as well as in the glands that are the seat of pathologic hypertrophy and hyperplasia, labyrinthine intercommunication of acini exists and is probably limited to the connection of primary with secondary acini. Solid masses of undifferentiated interfollicular epithelium are found in both normal and pathologic glands, but such masses are readily accounted for as detached extrafollicular buds. Evidence contrary to certain observations by Rienhoff concerning the mechanics of hyperplasia in the thyroid gland is presented.

AUTHOR'S SUMMARY

EXPERIMENTAL GLOMERULONEPHRITIS IN A MONKEY E T BELL and B J CLAWSON, *Am J Path* 7 57, 1931

A form of chronic diffuse glomerulonephritis was produced in a monkey by repeated intravenous injections of streptococci over a period of four years. The lesion was characterized histologically by marked increase in capillary endothelium and increase in the thickness and number of layers of capillary basement membrane. Histologically, the glomerular lesion resembled human "lipoid nephrosis of mixed type," except that no fat was present.

AUTHORS' SUMMARY

CHRONIC TYPHOID CHOLECYSTITIS F B MALLORY and G M LAWSON, JR,
Am J Path 7 71, 1931

The gallbladders of seven typhoid carriers are described. A common histologic picture was found (diffuse lymphocytic infiltration of mucosa, with focal accumulations in the form of typical lymph nodules). A review of 400 routine slides of chronic cholecystitis showed a similar lesion in 65 per cent of the cases. A review of the clinical histories showed that only 49 per cent of the cases with negative histories showed this picture as against 25 per cent of cases with positive histories. It is felt that the lesion described is characteristic of chronic typhoidal cholecystitis, but not pathognomonic of it. It is suggested that it is not specific of any organism, but represents a reaction to persistent infection of the bile in contrast to the more usual type of chronic cholecystitis with sterile bile and persistent infection of the wall.

AUTHORS' SUMMARY

INFECTIOUS CIRRHOSIS H E MACMAHON, Am J Path 7 77, 1931

Uncomplicated infectious cirrhosis is one of the rarer diseases of the liver. It is caused probably in most instances by the colon bacillus, and is characterized by variable proliferation of connective tissue and of bile ducts about the portal areas. Obstructive cirrhosis resulting from prolonged biliary obstruction is a much more common condition, although less conspicuous and hence frequently overlooked. Most cases of infectious cirrhosis are found in combination with obstructive cirrhosis, but even this combined type is relatively rare and is almost invariably fatal.

AUTHOR'S COMMENT

BIOLOGIC AND HISTOLOGIC STUDY OF LYMPH NODES IN SYPHILIS E SALEEBY
and S S GREENBAUM, J A M A 96 98, 1931

The inguinal lymph glands from twenty-one syphilitic patients were studied histologically and biologically. In five cases we were able to find *Spirochaeta pallida* in the sections, while in others only dark stained granules were observed. Of the animals into which the glands were transplanted, thirteen became infected after the first transplant and three after the second transplant. The organs from nine of the infected rabbits were studied histologically for spirochetes. The testes were infected in all the cases, the lymph glands in five and the heart and the aorta in two. Dark stained granules were present in most of the lymph glands and in the heart. *Spirochaeta pallida* was demonstrated in all sections of the testicles of the animals. In one animal, rabbit 8, we found fragments of the organism in all the sections. The heart showed them in two cases (8 and 3) and the lymph glands in five cases. Of the eight animals in which a second transplant was made, three became infected after eighty-one, seventy-two and sixty-three days. The remaining five became infected following the first transplant. The time varied from twenty-eight to eighty-seven days. Three rabbits became infected after the second transplant, and the remaining five were negative after the first and second transplants. The rabbits receiving injections of the human glands in which spirochetes were demonstrated "came up" in twenty-eight, forty-three, seventy, sixty-five and sixty-eight days. In comparing this series with the other we find little difference in the average number of days.

AUTHORS' SUMMARY

MILIARY PULMONARY DISEASE OF UNKNOWN NATURE R R SAYERS and F V MERIWETHER, Pub Health Rep 45 2994, 1930

On roentgen examination of miners a number of cases of discrete, shotlike spots in the lungs were noted. Others have referred to such cases as cases of miliary calcification of the lungs. Sayers and Meriwether found aspergilli in the sputum of miners with such miliary nodules in the lungs, and consequently they suggest that the nodules may be due to fungus infections.

ASBESTOSIS BODIES IN THE SPUTUM F W SIMSON and A S STRACHAN,
J Path & Bact **34** 1, 1931

The inhalation of asbestos dust in high concentrations leads to the appearance of asbestosis bodies in the sputum in a large percentage of the workers exposed thereto. They were present in forty-eight of fifty workers examined. Asbestosis bodies were as easily demonstrated by direct thick films as by the antiformin method. The sputum was always mucoid when there were no bronchial complications. It may resemble egg albumin. In none of the sputums were tubercle bacilli demonstrated. Study of the intracellular asbestosis bodies in these cases suggests that they are formed by the deposition on the asbestos fiber of an iron-containing substance elaborated by the cell.

AUTHORS' SUMMARY

EXPERIMENTAL LIVER NECROSIS FROM SHALE OIL C J POLSON, J Path &
Bact **34** 5, 1931

Necrosis of the liver was produced in rabbits and rats by the intraperitoneal administration of shale oil. By graduating the dose it was possible to produce all stages, from acute necrosis to cirrhosis. These lesions formed one continuous series and were almost indistinguishable from those of the "atrophic" series in man. The difficulties arising from the presence of naturally occurring disease were largely overcome by laparotomy and biopsy of the liver. Shale oil is clearly an active poison to the liver. Attention is drawn to the distinct differences between the action of the oil and that of its noncarcinogenic residue.

AUTHOR'S SUMMARY

MELANOSIS COLI M J STEWART and E M HICKMAN, J Path & Bact **34**
61, 1931

Melanos coli is due to the deposition of a melanin-like pigment within large mononuclear cells in the mucous membrane of the gut. It is limited in most cases to the large intestine and appendix, and ranges in intensity from gray or buff through dark gray or brown to inky black. Metastasis of pigment to the submucosa and mesocolic lymph glands may occur in the more advanced cases. The chief causative factor is chronic intestinal stasis, whether resulting from organic obstruction or from simple constipation. The more extreme grades are comparatively rare, but if the slighter forms are included, the incidence is fairly high, 11.2 per cent in an unselected series of 600 autopsies at all ages. In persons over the age of 40 the incidence is higher, 17.7 per cent, and in two series of cases of carcinoma of the colon it was 48.8 per cent and 55 per cent, respectively. In most of these the melanos was more intense above than below the growth. The most acceptable theory of the mode of formation of the pigment is Pick's—that aromatic products of the disintegration of proteins are absorbed from the colon and converted into melanin within the connective tissue cells by the action of a tyrosinase-like ferment.

AUTHORS' SUMMARY

COMPENSATORY HYPERTROPHY OF THE ADRENAL CORTEX IN THE RABBIT
E M MacKAY and W S POLLAND, J Path & Bact **34** 73, 1931

Removal of one adrenal in the rabbit is followed by compensatory hypertrophy of the remaining one due entirely to an increase in the size of the cortex. This compensatory hypertrophy is less than that following unilateral adrenalectomy in the rat.

AUTHORS' SUMMARY

MULTIPLE CONGENITAL SUBEPENDYMAL XANTHOMAS PIETRO REDAELLI, Arch
ital di anat e istol pat **1** 455, 1930

The author describes a case of hydrocephalus in a boy, 7 months old, with multiple congenital subependymal nodules in the lateral ventricles, which were

enormously dilated with a clear fluid. The nodules were of pinhead size and were composed of cells that contained refractory neutral fats and also fatty acids.

EMIL WEISS

CYANOSIS FROM SCLEROSIS OF THE PULMONARY ARTERY F SCHIASSI, Arch di pat e clin med 9 526, 1930

The author reports a case of chronic cyanosis due to sclerosis of the pulmonary artery with obliteration of the smaller branches.

E HAAM

INFARCTION DUE TO SCLEROSIS OF THE PULMONARY ARTERY AND THROMBOSIS G INVERNIZZI, Arch di pat e clin med 9 590, 1930

The author describes infarction of a whole lobe of the lung due to thrombosis in a large branch of the pulmonary artery, which was the seat of a primary sclerosis involving all the branches.

E HAAM

CONGENITAL MALDEVELOPMENTS OF THE DIAPHRAGM W PUTSCHAR, Beitr z path Anat u z allg Path 85 47, 1930

Putschar describes thirteen examples of complete defect of the diaphragm and two of diaphragmatic hernia. The two hernias were observed in children, one of the left side in a new-born female infant and a para-esophageal hernia in a child whose age or sex could not be determined from the preparation. Of the diaphragmatic defects, two were noted in adults and eleven in fetuses or infants. In only one case was the defect of the right side, in the remainder, it was of the left side. Only three of the thirteen subjects with defective diaphragms were males, in one of the two adults, the sex could not be determined from the specimen available. Four of seven female fetuses or infants with defects of the left side were anencephalic monsters, and one was a diprosopic monster. Of the three male fetuses or infants with defect of the left side, two were dicephalic. In the defect of the right side, the right lobe of the liver and parts of the large and small intestine were in the thoracic cavity. In the defects of the left side, the spleen, part of the stomach and parts of the large and small intestine were invariably in the thoracic cavity, in some of the cases the pancreas, the left lobe of the liver and the left kidney and suprarenal were also displaced into the thoracic cavity. Putschar discusses the various theories that have been propounded to explain the genesis of maldevelopments of the diaphragm, but believes that exact knowledge is still too incomplete to permit definite conclusions. The frequent association of other developmental anomalies, some of which, as absence of an umbilical artery in three of his cases, must have arisen before the formation of the diaphragm was initiated, incline him to place greater weight on abnormalities of the germ plasma than on purely mechanical factors in the genesis of diaphragmatic maldevelopments.

O T SCHULTZ

EOSINOPHILIA IN MALIGNANT ENDOCARDITIS W S BOIKAN, Folia haemat 42 164, 1930

There is reported a case of long standing allergic seasonal eczema, complicated by thrombo-endocarditis and showing marked eosinophilia. The postmortem observations were those of intense eosinophil granulopoiesis in the bone marrow and extensive infiltrations of mature eosinophils in the internal organs about embolic foci of necrosis. From the evidence adduced the conclusion is drawn that the eosinophilia of blood and tissue represented the purposeful response of a bone marrow modified by allergy.

AUTHOR'S SUMMARY

- * THE RELATIONSHIP BETWEEN THE CLINICAL PICTURE OF GRAVES' DISEASE AND THE HISTOLOGY OF THE THYROID GLAND E. MAYER and A. C. FURSTENHEIM, *Virchows Arch f path Anat* **278** 391, 1930

Forty-seven goiters removed by operation were examined, and the histologic structure was compared with the clinical observations. The macroscopic appearance of the glands, in regard to the diffuse or the nodular form of goiter, is regarded as being without significance. In twenty-three cases the condition was diagnosed clinically as severe Graves' disease, eight patients did not show any thyrotoxic symptoms, and fourteen were treated prior to operation with Lugol's solution.

Polymorphism of the acini, columnar epithelium and thin colloid were, in former years, fairly regular observations in Graves' disease. But since several years—about since the introduction of the preoperative administration of iodine—the most commonly observed change in Graves' disease has been the macro-follicular colloid goiter with some papillary proliferation of the epithelium. The height of the epithelium does not correspond to the grade of thyrotoxic symptoms. In severe Graves' disease the epithelium is occasionally cubical, and the walls of the alveoli are smooth and without papillations. In cases without hyperthyroidism, marked projections of the epithelial wall can be found.

There is a better relationship between the clinical symptoms and the staining quality of the colloid, especially when the methods of Mallory and Kraus are applied. After the administration of iodine, the histologic picture of hyperplastic glands seems changed, not so much in the appearance of the epithelium as in the quality of the colloid. Thyroid glands obtained from patients with exophthalmos did not differ from those from patients without involvement of the eyes.

C. A. HELLWIG

- COMPRESSION OF SPINAL CORD BY ARACHNOID CYSTS K. NICOLAISEN and M. HAALAND, *Norsk mag f laegevidensk* **91** 577, 1930

In a man, 45 years old, compression of the dorsal part of the spinal cord with resulting paralysis was relieved completely by enucleating four small cysts in the pia-arachnoid. The fluid in the cysts was clear, watery and free from parasitic elements, the walls were thin, fibrous and lined on the inner surface by a single layer of low cells. The nature of the cysts remained obscure.

- DISTRIBUTION AND DISAPPEARANCE OF CONGO RED AND GRANULAR STORAGE FACTORS OF THE RETICULO-ENDOTHELIAL CELLS Y. TAKEDA, *Jap J Exper Med* **8** 433, 1930

The distribution of dye-stuff varies according to the length of time after its injection. In the first period it is distributed to the blood and lymph and to the tissue, and is being excreted by the liver and kidney. In the second period the dye can no longer be seen in the blood stream. The isolated dye is excreted through the liver, concentrated to a visible degree. The amount of the injection, the interval of time after the injection and the functional state of the storing cells constitute the factors for the granular storage of congo red in the reticulo-endothelial cells. A close relationship exists between these factors.

EDNA DELVES

Pathologic Chemistry and Physics

- POSTOPERATIVE BLOOD CHEMISTRY E. ANDREWS and K. REUTERSKIOLD, *Ann Surg* **92** 786, 1930

Intensive postoperative chemical studies of the blood were made on patients from twenty-four to thirty-six hours after operation. There were no significant changes in the leukocytes, blood pressure, temperature, pulse rate, blood sugar,

water content, chlorides or carbon dioxide. Marked changes were found in the Aldrich-McClure test indicative of increased tissue thirst. Tests of permeability of the skin showed that this was much increased. Profound changes in the balance of mineral salt were noted. The potassium calcium ratio often fell below one. These changes per se may be considered adequate to account for the condition known as postanesthesia sickness.

AUTHORS' SUMMARY

ACETONE BODIES IN NORMAL PREGNANCY AND IN THE TOXEMIAS OF PREGNANCY. H. J. STANDER and J. F. CADDEN, Bull. Johns Hopkins Hosp. **47** 382, 1930.

The total acetone bodies (free acetone, diacetic acid and beta-oxybutyric acid) in the blood in normal nonpregnant women vary between 11 and 18 mg. of acetone per liter of blood, after correction for lactic acid, the average being 15.8 mg. In normal pregnancy the total corrected acetone bodies vary between 11 and 24 mg. per liter of blood, with an average slightly higher than in the nonpregnant woman (16.6 mg.). The total corrected acetone bodies in the blood of pregnant women with nephritis lies between 8.6 and 48.8 mg. of acetone per liter of blood. Eclampsia is accompanied by a definite elevation in the quantity of acetone bodies in the blood, averaging 50.2 mg. of acetone per liter of blood. The tendency toward ketosis in pregnant women may in part explain the lowered total base observed in their blood as term is approached. The increased acetone bodies in the blood of eclamptic patients may be a partial factor in producing the uncompensated deficit of alkali seen in that disease, although the accumulation of lactic acid is perhaps the major factor in the causation of the acidosis. A diet low in fats and high in carbohydrates seems indicated in normal pregnancy, and must certainly be of value in cases of toxemias showing evidence of ketosis.

AUTHORS' SUMMARY

THE ELIMINATION CURVE OF IODINE FROM THE BLOOD. H. EITEL and A. LOESER, Klin. Wchnschr. **10** 109, 1931.

The elimination curve of iodine from the circulating blood following the intravenous administration of sodium tetraiodophenolphthalein during ten hours is a regular decline. After ligation of the ductus choledochus, there is an initial decline and then a marked delay in the elimination of iodine. After ligation of the cystic duct, there is an irregular elimination of iodine, so that a steplike curve is formed.

AUTHORS' SUMMARY

TRACES OF MERCURY IN THE URINE AND FECES. PAUL BORINSKI, Klin. Wchnschr. **10** 149, 1931.

The excrements of 51 per cent of seventy-five persons having no contact with mercury contained this metal. The daily excretion was from 5 to 10 γ ($\gamma = 0.001$ mg.). The same daily excretion of mercury was observed in persons with old amalgam fillings. Those with recent fillings, as well as those otherwise coming in contact with mercury, eliminated appreciably more. Practically all foods contain small traces of mercury, the amount ingested daily in food is estimated at 5 γ , an amount equal to that eliminated by persons having no contact with mercury or carrying old amalgam fillings. The average daily excretion of from 5 to 10 γ is considered normal and does not indicate poisoning with mercury.

AUTHOR'S SUMMARY

THE SPECIFIC GRAVITY OF THE BLOOD AND ITS CONSTITUENTS. C. OESTREICH, Klin. Wchnschr. **10** 160, 1931.

The specific gravity of the whole blood varies from 1.050 to 1.060, and that of the plasma, from 1.025 to 1.026. In anemia, the specific gravity of the whole blood diminishes, it was observed as low as 1.030. A high specific gravity (from

1 095 to 1 100) of the red cells was observed in pernicious anemia. A specific gravity of the erythrocytes of over 1 095 indicates pernicious anemia, the normal is from 1 085 to 1 094.

AUTHOR'S SUMMARY (IN PART)

THE CHOLESTEROL OF THE BLOOD IN HYPERTENSION C. ALVAREZ and S. M. NEUSCHLOSZ, *Klin Wchnschr* **10** 244, 1931

The serum of normal persons is unsaturated (from 50 to 90 per cent) with reference to cholesterol. In hypertension it is supersaturated (from 106 to 132 per cent). Among twenty-five patients with hypertension, only four were without this change.

AUTHORS' SUMMARY

Microbiology and Parasitology

THE ETIOLOGY OF RHEUMATOID ARTHRITIS RUSSELL L. CECIL, EDITH E. NICHOLLS and WENDELL J. STAINSBY, *Am J M Sc* **181** 12, 1931

The evidence for the streptococcal origin of rheumatoid arthritis may be summarized as follows. Almost constant presence of streptococci in foci of infection. Streptococci recoverable from blood in 62.3 per cent of rheumatoid patients, 3.9 per cent in pathologic controls, none in healthy controls. Streptococci recoverable from affected joints in 67.3 per cent of rheumatoid patients, from blood or joint in 77 per cent, none from nonrheumatoid joints. High agglutination of "typical strains" of streptococci with serums of 94 per cent of patients with rheumatoid arthritis. Disappearance of agglutinins with recovery from systems of arthritis. Biologic identity of streptococci recovered from blood, joint and focus of infection in the same patient, though there have been a number of exceptions to this rule. Reproduction of rheumatoid arthritis in rabbits with "typical strains" of streptococci. Recovery of same streptococci from blood and joints of arthritic rabbits. Striking similarity of histologic changes in rabbits' joints to those in human rheumatoid joints.

AUTHORS' SUMMARY

BRUCELLA INFECTION WITH RECOVERY OF BRUCELLA FROM THE BILE HUGH R. LEAVELL and HAROLD L. AMOSS, *Am J M Sc* **181** 96, 1931

A case is described in which *Brucella* was recovered from the bile removed by duodenal drainage, and from the contents of the gallbladder at operation. In a patient whose extirpated gallbladder contained *Brucella*, the stools, from which *Brucella* was isolated prior to operation, no longer showed these organisms following cholecystectomy.

AUTHORS' SUMMARY

STUDIES ON THE VIRUS OF FOWL-POX E. W. GOODPASTURE, A. M. WOODRUFF and C. E. WOODRUFF, *Am J Path* **6** 699 and 713, 1930

Fowlpox virus in suspensions of finely divided material is rendered inactive after a period of from four to twenty-four hours in 1 per cent potassium hydroxide. In the form of inclusion bodies, however, the virus is found to be infectious, in diminishing strength, after treatment with potassium hydroxide for as long as five days. No evidence has been found for the existence of a nucleoprotein toxin, such as that described by Sanfelice, either in scabs of the fowlpox lesion or in digested inclusion bodies. The destructive action of 1 per cent potassium hydroxide on normal epithelial cells of the chick is shown. The presence of Borrel bodies in inclusion which have been proved infectious after remaining twenty-four hours in 1 per cent potassium hydroxide has been demonstrated.

Inclusion bodies of fowlpox may be broken up by using the surface tension of a drying film of water. The stained smear of an inclusion body thus disrupted has been shown to contain as many as 20,000 Borrel bodies—minute coccoid structures uniform in size and shape. Multiple inoculations have been made from

the smears of isolated and ruptured inclusion bodies with as many as six inoculations from a single inclusion resulting successfully. Control inoculations were all negative. The lipid component of the inclusion bodies is noninfectious. Aside from this lipid, the Borrel bodies form the major constituent of the inclusions and are judged to represent the actual virus of fowlpox.

AUTHORS' SUMMARIES

THE INCLUSION BODIES OF FOWL-POX AND MOLLUSCUM CONTAGIOSUM E. W. GOODPASTURE and C. E. WOODRUFF, *Am J Path* **7** 1, 1931

The inclusion bodies of molluscum contagiosum may be freed from surrounding cellular material by tryptic digestion. Unlike fowlpox inclusions, the molluscum bodies are found to be sticky and gelatinous after they have been digested. Because of this characteristic they cannot be manipulated readily with the Chambers microdissection apparatus. The gelatinous matrix of the molluscum bodies has a markedly granular appearance owing to the presence within it of myriads of Lipschutz granules—minute coccoid structures 0.25 micron in diameter. These granules are identical in size, shape and staining reactions with the Borrel bodies of fowlpox. They are resistant to the action of trypsin. On being placed in distilled water, the inclusion bodies of molluscum show little or no swelling. Under similar conditions the fowlpox inclusions swell markedly, owing, probably, to their lipid material acting as a semipermeable membrane. Trituration of the molluscum inclusions readily breaks them up into the component Lipschutz granules. Fowlpox inclusions, similarly treated, fail to break up so readily into Borrel bodies. This difference in the reaction of molluscum and fowlpox to trituration may afford an explanation for the relatively greater filtrability of the former. Fowlpox and molluscum contagiosum are apparently specific for fowls and man, respectively; cross-inoculation experiments having proved unsuccessful. Attempts to transfer molluscum to monkeys and other laboratory animals were also unsuccessful.

AUTHORS' SUMMARY

EXPERIMENTAL EFFORTS TO TRANSFER MONKEY MALARIA TO MAN HERBERT C. CLARK and LAWRENCE H. DUNN, *Am J Trop Med* **11** 1, 1931

We conclude that red spider monkey malaria and the human benign species of malaria that it so closely resembles are not identical, and that the monkey is not therefore, a reservoir for human malaria, in view of the fact that in two control monkeys of different species from the red spider monkey acute attacks of malaria developed on schedule time (eleven days) and that no symptoms and no satisfactory laboratory observations developed in eight men representing the best type of nonimmune subjects. It remains to be seen, however, what may happen when an infant monkey (born free from opportunities to acquire monkey malaria) is inoculated with human malaria of the benign species. We await this opportunity, but circumstances indicate that it will not acquire the disease. The knowledge gained by our local field and laboratory work on monkeys offers one practical feature. The infant and juvenile monkeys of certain species (*Ateles* and *Cebus*) offer a better animal for research in malaria than the bird, which is customarily used. It is interesting to note that two specimens of *A. taysimaculatus* and one specimen of *A. albimanus* fed on the monkeys showed positive glands on dissection. Further work is indicated in feeding mosquitoes on monkey malaria since it may at least assist in providing teaching material.

AUTHORS' SUMMARY

STUDIES ON YELLOW FEVER IN SOUTH AMERICA NELSON C. DAVIS and RAYMOND C. SHANNON, *Am J Trop Med* **11** 21, 1931

Aedes fluviatilis has been found to transmit yellow fever virus under laboratory condition. As few as three insects have produced a fatal infection by feeding on a rhesus monkey. *Aedes taeniorhynchus* has proved to be a less efficient

host than *Aedes fluviatilis*. However, in one instance a fatal infection of yellow fever resulted from the bites of this species. No transmission of yellow fever has been secured by the bites or by the injection of *Sabethini* mosquitoes. It is thought that in one instance yellow fever virus remained alive in the bodies of *Triatoma megista* for one week. However, the experiments with *Triatoma* have been rather inconclusive.

AUTHORS' SUMMARY

THE TRANSMISSION OF YELLOW FEVER NELSON C DAVIS, Am J Trop Med
11 31, 1931

Stegomyia mosquitoes captured in houses in Sao Salvador, Bahia and Brazil did not produce yellow fever when injected into *Macacus rhesus*. Mosquitoes that had already digested a meal of immune blood gave rise to no immunity when injected into or fed on rhesus monkeys. Mosquitoes that had already digested one or more meals of immune blood became infective after feeding on an animal with yellow fever. In mosquitoes that had already digested a meal of infectious blood, the ingestion of immune blood had no influence on the subsequent development of infectivity. Two batches of mosquitoes that fed on a mixture of infectious blood and immune serum did not become infective. The mixture itself produced yellow fever when injected directly into a monkey. A similar blood mixture with saline solution substituted for the immune serum proved infectious on direct inoculation and gave rise to infectivity on ingestion by two batches of mosquitoes. Mosquitoes that took an interrupted meal, first on an immune monkey and immediately afterward on an infected monkey, developed infectivity. A similar lot, which fed first on the infected and secondly on the immune animal, produced no disease when injected into a rhesus monkey. However, the monkey was subsequently immune to a test dose of virus.

AUTHOR'S SUMMARY

OCULAR LESIONS OF RAT-BITE FEVER IN GUINEA-PIGS S BAYNE-JONES and
M L LERNER, Arch Ophth 4 858, 1930

Lesions of the eyes and contiguous structures occurred in about 60 per cent of guinea-pigs infected with *Spirochaeta morsus-muris*. The infection is reproducible with regularity in these animals and provides a convenient method for the investigation of ocular lesions occurring in the course of a systemic infection. The lesions vary in intensity during the course of the disease, but are generally severe at the time when the animals are moribund. The infection produces blepharitis, conjunctivitis, interstitial keratitis with corneal ulceration and moderate iritis and cyclitis. Characteristic cellular infiltrations occur also in the lacrimal glands, chiefly around the ducts, and in the perivascular regions in the external ocular muscles. Spirochetes were found in the conjunctival exudate, but could not be demonstrated with certainty in the cornea.

AUTHORS' SUMMARY

THE ACTION OF LOW-VELOCITY ELECTRONS ON MICROORGANISMS D A
WELLS, Bull Basic Sc Research 3 5, 1931

Staphylococcus albus is killed when exposed to a beam of low velocity electrons. When the total energy is maintained at a constant value, there is a rapid rise in the percentage of killing within the range of from 25 to 30 volts. The results indicate that the lethal action is a function of the energy of the individual electrons.

C E CLIFTON

THE INCREASED BACTERICIDAL EFFECT OF INORGANIC COMPOUNDS IN THE
PRESENCE OF X-RAYS R F NORRIS, Bull Basic Sc Research 3 19, 1931

When bacteria are irradiated with x-rays in solution containing various inorganic salts, the resulting lethal action is much greater than that obtained by

exposing the bacteria successively to x-rays and to the salts previously irradiated. Evidence is given to indicate that this is a true synergistic action and not primarily due to ultraviolet fluorescence, or to emission of photo-electrons.

C E CLIFTON

THE CELLS FOUND IN TUBERCULOUS TISSUES ON VITAL AND SUPRAVITAL STAINING. E H TOMPKINS and R S CUNNINGHAM, Bull Johns Hopkins Hosp 48 8, 1931

Tissues from tuberculous guinea-pigs were stained vitally with trypan blue. The tissues were examined both by sections of fixed material and by scrapings stained supravitaly. The large mononuclear cells found in the tuberculous areas consisted of monocytes, clasmatocytes and epithelioid cells, together with transitional and degenerate forms of the same cells. Only a few of the monocytes contained trypan blue, although they stained vigorously with neutral red. The clasmatocytes always contained trypan blue in great amounts. The number of epithelioid cells that contained the vital dye and the amount of dye within them varied considerably. By means of the superimposition of the supravital on the vital dye, transitions could be followed from clasmatocytes to epithelioid cells, as well as from monocytes to epithelioid cells. The types of staining observed in the giant cells were analogous to those observed in the mononuclear cells. The concept has been developed that, in tuberculosis, some toxic factor, acting either from within or from without the cells, affects the functions of both the monocytes and the clasmatocytes, so that these cells become modified both in morphology and in activity, and develop into characteristic epithelioid cells or into giant cells, or die and degenerate at any stage in the course of these changes.

AUTHORS' SUMMARY

CONTROL OF INTESTINAL PUTREFACTION IN MAN BY DI-HYDRANOL. V LEONARD and W A FEIRER, Bull Johns Hopkins Hosp 48 25, 1931

Intestinal putrefaction is usually a mild and irregular phenomenon, although instances in which it may be a constant and fairly active process are by no means uncommon. Since the organisms of true putrefaction are spore-bearers, the putrefactive properties of the stools may be taken as a measure of intestinal putrefaction. The presence or absence of intestinal putrefaction in a given case as well as its intensity may therefore be proved by simple, direct, bacteriologic methods. The administration of di-hydranol (2-4-dihydroxyphenyl n-heptane) in doses of from 0.3 to 0.45 Gm, three times daily, destroys the true putrefactive flora of the intestinal tract with great certainty and regularity.

AUTHORS' SUMMARY

EXPERIMENTAL SYPHILIS. A M CHESNEY and T B TURNER, Bull Johns Hopkins Hosp 48 90, 1931

When rabbits are inoculated with syphilitic virus in such a manner as to produce a lesion involving the skin, whether the original inoculation is made subcutaneously, intracutaneously or by depositing the virus on the surface of a granulating wound, subsequent inoculation with homologous virus after a period of four months or more is not followed by the development of lesions, no matter whether the second inoculation is made intratesticularly, subcutaneously, intracutaneously or intravenously. Under these conditions, intravenous reinoculation may be followed by reinfection without lesions. When syphilis develops in rabbits after intratesticular inoculation, a second inoculation with homologous virus by the intracutaneous route after a period of four months or more is not followed by the development of any lesions at the site of inoculation. When syphilitic virus is injected intravenously into rabbits, marked and widespread lesions of the skin and bones develop. When these animals are reinoculated with homologous virus

after a period of several months, whether by subcutaneous or by intracutaneous injection, no lesions develop. However, intravenous injection under these circumstances may be followed by reinfection, but without lesions. The bearing of these facts on the distribution of acquired resistance in syphilis is discussed.

AUTHORS' SUMMARY

THE GERMICIDAL ACTION OF α -MERCAPTO AND α -DISULFO SOAPS. A. H. EGGERTH, J. Exper. Med. **53** 27, 1931.

Certain of the α -mercapto soaps and α -disulfo soaps are powerful germicides. In the α -mercapto series, the soaps with 12 and 14 carbon atoms are most germicidal. In the disulfo series, the dicaprato, dilaurate and dimyristate are most germicidal. The optimum number of carbon atoms varies with the test organism used. These soaps, like others previously studied, show a markedly selective germicidal action.

AUTHORS' SUMMARY

THE ACTION OF TESTICULAR, KIDNEY, AND SPLEEN EXTRACTS ON THE INFECTIVE POWER OF BACTERIA. M. PIJOUAN, J. Exper. Med. **53** 37, 1931.

The addition of testicle extract to cultures of twenty different bacteria just prior to inoculation enhances their infectious activity to a high degree. Kidney extracts enhance the infections of staphylococci to a less degree than testicle extracts, while spleen extracts never give rise to enhancement and often cause the lesion to be less severe than would ordinarily be the case.

AUTHOR'S SUMMARY

THE EFFECT OF TESTICULAR EXTRACT ON FILTRABLE VIRUSES. D. C. HOFFMAN, J. Exper. Med. **53** 43, 1931.

The Reynals factor promotes the pathogenic action of the viruses of herpes, vesicular stomatitis of horses, Borna's disease and vaccinia. The heightening of virulence is revealed in various ways. The effects of the viruses may be accentuated, a weak strain may be converted into a strong one, as in the case of the F strain of herpes virus, or power may be acquired to infect resistant species or tissues, such as rabbits and the abdominal skin of guinea-pigs, with acute vesicular stomatitis. The Reynals factor should serve as an important agent in the study of filtrable viruses.

AUTHOR'S SUMMARY

THE TOXIC PROPERTIES OF TUBERCULO-PROTEINS AND POLYSACCHARIDES. F. R. SABIN, F. R. MILLER, C. A. DOAN and B. K. WISEMAN, J. Exper. Med. **53** 51, 1931.

The temperature reaction in tuberculous and normal guinea-pigs and rabbits is elicited by the tuberculo-protein and probably not at all by the polysaccharides. The polysaccharides may have some killing power under certain conditions, but this is not as consistently related to dosage as in the case of the proteins. Both proteins and polysaccharides cause a change in the white blood cells when introduced by any route.

AUTHORS' SUMMARY

AN ACCELERATED FEBRILE REACTION IN MONKEYS UPON REINOCULATION WITH POLIOMYELITIS VIRUS. C. W. JUNGEBLUT, J. Exper. Med. **53** 159, 1931.

As a rule, primary poliomyelitic infection in the monkey, is not characterized by a significant increase in the temperature of the body during the incubation period until forty-eight or twenty-four hours before the onset of clinical symptoms, when a critical rise of the temperature occurs. On intracerebral reinoculation, the temperature curve of recovered monkeys shows an almost immediate and

marked febrile reaction during the first twenty-four or forty-eight hours after inoculation. A similar accelerated febrile reaction may be obtained in recovered animals after subcutaneous injection of killed virus. In case the previous infection is of recent date, reinoculation may not lead to demonstrable reaction. Monkeys that have received a number of parenteral injections of live virus respond to intracerebral infection with a precocious and prolonged febrile reaction on the third or fourth day after infection, which may last until the onset of symptoms. The altered response to reinoculation of monkeys that have previously been in contact with the virus suggests a close analogy with the accelerated reactions observed in allergic phenomena.

AUTHOR'S SUMMARY

LESIONS IN THE CENTRAL NERVOUS SYSTEM IN HOG CHOLERA O SEIFRIED,
J Exper Med **53** 277, 1931

A more or less marked encephalomyelitis and meningitis was found in thirty-three of thirty-nine cases of virus hog cholera in which the animals had been infected either intramuscularly or by contact and killed between six and forty-nine days after infection. This hog cholera encephalitis is characterized by a varying amount of vascular and perivascular infiltration with small lymphocytes, mononuclear elements, a few plasma cells and occasionally a few eosinophilic leukocytes. The glia shows a proliferation surrounding infiltrated vessels or forming small nodules or more diffuse foci. Satellitosis and, in a few instances, true neuronophagia have been observed. Both microglia and macroglia participate in this process. There is no essential increase of glia fibers. In nearly all parts of the central nervous system degenerating lesions of the nerve cells, such as tigrolysis and degeneration of the nucleus, including a slight atrophy of endocellular neurofibers, are encountered. No demyelination has been observed. Specific inclusion bodies in the nerve cells are absent. In addition, in a certain number of cases microscopic and macroscopic hemorrhages are present in the brain, spinal cord and meninges. These lesions, in varying degrees, have been found in swine infected with four different strains of hog cholera virus. Two were laboratory strains and two were obtained from fresh field outbreaks. Histologic changes in the central nervous system were found as early as six days after infection before the animal showed symptoms in the central nervous system. In two cases in which the animals were paralyzed, no lesions could be demonstrated in the central nervous system. The lesions in the central nervous system are considered to be the anatomic substratum for the various nervous symptoms commonly found in hog cholera.

AUTHOR'S SUMMARY

THE VIABILITY OF BOVINE TUBERCLE BACILLUS ON PASTURE LAND, IN STORED
FAECES AND IN LIQUID MANURE R STENHOUSE WILLIAMS and W A
HOY, J Hyg **30** 413, 1930

Under ordinary conditions in the south of England, *B. tuberculosis* may remain alive and virulent in cow feces exposed on pasture land for at least five months during winter, for two months during spring and for four months during autumn. In summer no living organisms were demonstrated after two months. Under special conditions, e. g., protection from direct sunlight, the survival period may be four months during the summer. In the autumn, feces protected from earthworms, etc., yielded bacilli after six months. Living and virulent tubercle bacilli were found after twelve months' storage in the naturally infected feces, and for a period of at least two years in the artificially infected feces. Living and virulent tubercle bacilli were found in stored liquid manure at least four months after infection. During this time a gradual diminution of the virulence of the material was observed.

AUTHORS' SUMMARY

THE PATHOLOGY OF GENERALIZED VACCINIA IN RABBITS RALPH D LILLIE
and CHARLES ARMSTRONG, Nat Inst Health Bull, 1930, no 156

An account of the pathologic histology of local and focal lesions of the skin, mucosæ and viscera of rabbits produced by Armstrong's heat-selected vaccine virus is detailed. The literature of the histology of variola and vaccinia is reviewed. The visceral lesions are essentially coagulation necroses, those of the skin and mucosæ also show coagulation necrosis in addition to various other proliferative, degenerative, hemorrhagic and inflammatory changes. The distribution of such focal lesions is summarized in tabular form according to organs and by routes of inoculation and lapse of time after inoculation.

AUTHORS' SUMMARY

BACILLUS PSITTACOSIS NOCARD, 1893 FAILURE TO FIND IT IN THE 1929-30
EPIDEMIC IN THE UNITED STATES SARA E BRANHAM, GEORGE W MCCOY
and CHARLES ARMSTRONG, Pub Health Rep 45 2153, 1930

During the recent outbreak of psittacosis in the United States, an intensive search for the '*Bacillus psittacosis*' of Nocard was made in the carcasses and droppings of parrots that were shipped to the National Institute of Health, in experimentally infected and in normal parrots and parakeets, and in material obtained from human cases. No strain of "*B psittacosis*" or of any other member of the *Salmonella* group of bacteria was found. In fifty-seven convalescent serums studied, agglutinins for "*B psittacosis*" and other *Salmonella* bacteria were not demonstrable in dilutions that could be considered significant. We have found no evidence of the association of any member of the *Salmonella* group of micro-organisms with psittacosis either in birds or in man.

AUTHORS' SUMMARY

THE TRANSMISSIBILITY OF TICK-BITE FEVER VIRUS TO GUINEA PIGS
ADRIANUS PIJPER and HELEN DAU, Brit J Exper Path 11 287, 1930

We believe we have shown that it is possible to transmit the virus of South African tick-bite fever to guinea-pigs. The animals react with a rise of temperature. In one instance, we have reached the fifth animal passage. Passages seem to increase the virulence. At postmortem examinations of our animals we have looked for, but have not found, evidence that perhaps some other, accidental, infection had been transmitted by us. Our temperature curves resemble those usually recorded, and regarded as typical, for guinea-pigs infected with *Rickettsia* virus (typhus and spotted fever of the Rocky Mountains). On these, and other grounds, also given in this paper, we conclude that South African tick-bite fever is caused by a living virus of the *Rickettsia* class.

AUTHORS' SUMMARY

CHANGES IN THE CENTRAL NERVOUS SYSTEM OF MONKEYS DUE TO VACCINE
LYMPH P A CLEARINK, Brit J Exper Path 11 329, 1930

Perivascular lesions have been found in the central nervous system of a large number of wild African monkeys after intradermic inoculation with vaccine lymph. The severity of the lesion depends to some extent on the dosage. The histology of the severe lesions is similar to that of postvaccinal encephalitis in man. This supports the view that vaccinia is the cause of postvaccinal encephalitis.

AUTHOR'S SUMMARY

A SALMONELLA CAUSING ABORTION IN SHEEP R LOVELL, J Path & Bact
34 13, 1931

Several strains of *Bacterium abortus-ovis*, a *Salmonella* organism causing epidemic abortion in sheep, have been studied in regard to their morphology, cultural and fermentation reactions and antigenic structure. The British strains

and the one of German origin ferment dextrose, maltose, mannite, xylose and dulcitol, with the production of gas. All of the strains studied failed to attack lactose, sucrose, salicin, inositol, rhamnose and, with rare exceptions, arabinose. All of the strains produced hydrogen sulphide slowly. The antigenic structure of the five British strains and the one German strain appears to be identical. As regards the "H" (flagellar) agglutinogens, *Bact abortus-ovis* is diphasic. The main component of the type phase is shared with *Bact paratyphosum C*. With regard to the group phase, an important factor is shared with *Bact paratyphosum C* and the related varieties, but there is also an additional component that appears to be peculiar to *Bact abortus-ovis*. The "O" (somatic) antigens are shared with *Bact abortus-equi* and the Reading and Derby types. One of the minor factors is shared with *Bact enteritidis*.

AUTHOR'S SUMMARY

OBSERVATIONS ON TROPICAL TYPHUS IN THE FEDERATED MALAY STATES
R LEWTHWAITE, Bull Inst M Research, Federated Malay States, 1930, no 1

Tropical typhus differs from the typhus of the western world in two ways. It is not louse-borne and it does not flare up in devastating epidemics. Two types are described, the "K" or "rural" and the "W" or "urban". These types are distinguishable only by epidemiologic and serologic methods. Tropical typhus is an acute infectious disease characterized by an abrupt fever and severe headache. A rash, macular and papular, appears after about five days, and the crisis appears at the end of the second week. Clinically, it resembles typhus exanthematicus, but epidemiologically it resembles other typhus-like fevers of the tropical region. It is a disease of inland towns and the countryside, the greatest percentage being of the "rural" type. Occupation greatly influences the incidence, and very few children are infected. The incidence is higher in males than in females. All cases, but one, gave positive Weil-Felix reactions. An excellent discussion of signs and symptoms, morbid anatomy and histopathology is included. In the study of the epidemiology of tropical typhus, little seasonal variation was found. Also, it was found that the "urban" type was largely a disease of indoor workers, while the "rural" type attacks those whose occupation involves contact with the countryside, especially the waste land overgrown with underbrush.

EDNA DELVES

EXPERIMENTAL TROPICAL TYPHUS IN LABORATORY ANIMALS R LEWTHWAITE,
Bull Inst M Research, Federated Malay States, 1930, no 3

In only a small number of cases does the inoculation of the tropical typhus virus cause a febrile reaction in guinea-pigs. Rats were found more susceptible. The intraperitoneal inoculation of infected human blood into rats produced a febrile reaction, but the results were not constant. A fever did not develop in all of the rats thus treated. However, in those in which a fever did develop, the postmortem changes were fairly constant. Enlargement of the spleen was found in most of the rats in which a fever developed. In one of the five rats examined histologically, perivascular infiltration and typhus "nodules" were found in the brain. In another of the five cases, clumps of short diplobacilli with tapering ends were found in the brain. They seem to resemble the "diphtheroid" in morphologic appearance. Three of the eleven rabbits tested gave positive Weil-Felix reactions after being inoculated with infected human blood.

EDNA DELVES

SEPTINEURITIS IN NEUROTROPIC VIRUSES S NICOLAU, O DIMANCESCO
NICOLAU and I A GALLOWAY, Ann de l'Inst Pasteur 43 1, 1929

Septineuritis refers to the general spread of neurotropic viruses by way of the central, visceral or peripheral nervous system, with lesions in the trunks and finer nerve endings. Experimentally, it may be reproduced in animals with the

virus of encephalomyelitis or Borna's disease, smallpox, herpes, poliomyelitis and fixed or street rabies virus. The histologic picture (two color plates and twelve figures) is stated to show definite dissemination with accompanying lesions by way of the nervous system. The report is eighty-eight pages in length.

M. S. MARSHALL

POLIOMYELITIS IN ROUMANIA IN 1927. G. MARINESCO, M. MANICATIDE and S. DRAGANFSCO, *Ann de l'Inst Pasteur* **43** 223, 1929.

More than 1,500 cases are reported, they were studied clinically, therapeutically and from the standpoint of gross and cellular pathologic changes. The morbidity showed a peak in incidence between the ages of 1 and 3 years (61.9 per cent), and a ratio of 3:2 in males over females, the mortality was around 95 per cent. The report covers fifty-five pages and is quite complete.

M. S. MARSHALL

VARIABILITY IN SKIN FUNGI. R. BILTRIS, *Ann de l'Inst Pasteur* **43** 281, 1929.

In an article of 61 pages a mycologic study, accompanied by seventy-nine photographs, is presented on the characteristics of the dermatophytes. The question of morphologic and cultural variation is emphasized, particularly in the *Trichophyton* genus.

ENCEPHALOMYELITIS PROVOKED BY *TOXOPLASMA CUNICULI*. C. LEVADITI, V. SANCHIS-BAYARRI, P. LEPINE and R. SCHOEN, *Ann de l'Inst Pasteur* **43** 673, 1929.

Toxoplasmic encephalomyelitis in rabbits may run a chronic course in which the neuraxon continues to be contaminated by encysted *Toxoplasma* (schizonts), resembling the parasitic cysts described in human hydrocephalus (Jankû), toxoplasmic encephalomyelitis in mice may also evolve chronically. Certain animals live for 165 days and appear normal in spite of intense alterations of which the neuraxon is the seat, and although they are carriers of organisms virulent for the rabbit. (Sixty-two pages, with seven figures in color.)

AUTHORS' CONCLUSIONS

ENCEPHALOMYELITIS PROVOKED BY *TOXOPLASMA CUNICULI*. C. LEVADITI, V. SANCHIS-BAYARRI, P. LEPINE and R. SCHOEN, *Ann de l'Inst Pasteur* **43** 1063, 1929.

The study of encephalomyelitis induced in the rabbit, guinea-pig, pigeon, mouse and rat by *Toxoplasma cuniculi* furnishes particularly interesting results with reference to human pathology. It is correlated with certain etiologic problems in the domain of neuropathology, particularly those related to hydrocephalus and to certain hereditary congenital encephalites. The certainty of penetration of some of these protozoa in the cytoplasm of the neurons (neuroprotozooses) is furnished by the statements summarized in our articles. It renders more and more reasonable the microsporidian nature of the rabies virus, the Negri bodies of which represent, according to us, evolutionary phases (pansporoblastic phase) of *Gluglea lyssae* (Levaditi, Nicolau and Schoen). Finally, our investigations permit an explanation of the mechanism of immunity acquired from the neuraxon as exclusively a tissue immunity, eminently vital and independent of the parasitocidal properties of humoral substances.

AUTHORS' CONCLUSIONS

VACCINE VIRUS IN THE MONKEY. H. ALDERSHOFF, A. B. F. A. PONDMAN and A. W. POT, *Ann de l'Inst Pasteur* **43** 1268, 1929.

The brain of the *Cynomolgus* monkey responds to different vaccine viruses. Neurovaccine has no particular affinity for the neural axis of this animal. The virus may be cultivated in the brain without loss of virulence. Monkeys may be

vaccinated so effectively that intracerebral inoculation causes no trouble. Animals refractory to an intracerebral injection of neurotropic rabbit virus (from an infant dying of postvaccinal encephalitis) succumb, after an intracerebral reinjection with a fixed virus, to a paralysis caused by the latter. The hemorrhagic reaction, produced following cutaneous vaccination with neurotropic rabbit virus, is not a typical characteristic of this virus, but is observed also after cutaneous vaccination with the vaccine virus cultivated in the testicles of rabbits or in the brain of the monkey. We presume that this hemorrhagic reaction is a specific property of all vaccine viruses cultivated in tissues other than the skin. This factor will be investigated further. (Comment is made on this paper by C. Levaditi, *ibid*, p. 1512.)

AUTHORS' CONCLUSIONS

THE LYMPHOCYTE-MONOCYTE RATIO IN TUBERCULOUS INFECTION T. DE SANCTIS MONALDI, *Ann de l'Inst Pasteur* 44 70, 1930

The injection of filtrates ("ultravirus") of tuberculous material, active bacilli, heated ultravirus (80 C), tuberculin and BCG into guinea-pigs was followed by hematologic studies. The author concludes: The blood picture in animals inoculated with ultravirus should be divided into two types, one in which the lymphocyte-monocyte ratio remains high in animals overcoming infection, and the other with a descending ratio in dying cachectic animals, with enlarged lymph nodes in which acid-fast organisms are shown by repeated passage. The white cell count and the lymphocyte-monocyte ratio of the latter group are similar to those of guinea-pigs given injections of virulent organisms. With BCG, the picture simulates conditions obtaining in animals recovering from infection with ultravirus. The lymphocyte-monocyte ratio may double within two or three months, indicating a good prognosis. A large number of nonmotile cells are produced during the marked leukocytosis and cachexia in animals succumbing to virulent organisms or to ultravirus. Some days before death, in these animals (only), monocytes appear, with a small central roset and vacuoles dispersed through the protoplasm. The great number of nonmotile cells and these distinctive monocytes do not appear in animals inoculated with tuberculin or with BCG. The leukocyte reactions in animals inoculated with tuberculin or with heated ultravirus present quite a different picture from that described.

M. S. MARSHALL

Tumors

BENIGN POLYMORPHOCYLLULAR TUMORS OF THE KNEE REGION W. C. HUNTER, *Am J Path* 7 13, 1931

Two instances of benign polymorphocellular tumors occurring in the region of the knees of closely related persons are described. In the daughter, the new growth originated in the synovial membrane, a rare site of formation of a tumor, and was benign. In the father, the tumor was of exceptionally long duration, attained bulky dimensions and although exhibiting locally destructive properties also appeared to have been benign. Because of the large size and extensive ramifications of the mass, the point of origin could not be determined, but certain facts point to an extra-articular source. Most commonly new growths of the type herein reported arise from the sheaths of tendons and only rarely from the capsule or synovial membrane of the joints. In the latter event the knee is much more frequently involved than any other joint in the body. The rarity of such growths in the joint is evidenced by the fact that the author was able to collect from the literature, in addition to his own cases, only forty-four instances of closely similar or identical tumors.

AUTHOR'S SUMMARY

HYPERNEPHROMA WITH TUMOR THROMBOSIS OF VENA CAVA AND HEART S. H. POLAKIS and H. TART, *Am J Path* 7 63, 1931

This is the fifth case of hypernephroma with malignant thrombosis by invasion of the inferior vena cava and the heart. It is unique in its extent of involvement. The entire inferior vena cava and all its main tributaries (iliac, renal and hepatic veins) were occluded by a continuous malignant thrombus which extended into the right atrium, through the tricuspid valve into the right ventricle. The cardiac involvement here was even more extensive than in the case described by Weber, in which the thrombus did not extend beyond the right atrium. Another interesting feature was the fact that in spite of the massive involvement of the inferior vena cava and the right kidney, the right adrenal gland remained singularly free from metastasis.

AUTHORS' SUMMARY

RESISTANCE AND SUSCEPTIBILITY TO CANCER W. CRAMLER, *Ann Surg* 93 20, 1931

At its inception cancer is beyond doubt a local disease that arises in a limited area of cells subjected to chronic irritation. However, the process of cancerization is one that does not arise merely as the result of a direct action of a carcinogenic agent on epithelial cells, but it is much more complex. In fact, the local development of a malignant condition is influenced by factors that do not reside in the epithelial cells, but in the organism and exert their activity presumably through the system of the mesenchymal cells. The terms "susceptibility to cancer" and "resistance to cancer" are intended to embrace the activity of these factors. Furthermore, the study of these factors may enable one to modify their activity in such a way as to delay, or even to prevent, the inauguration of a cancer.

B. M. FRIED

HEREDITY AND CANCER H. T. DELLMAN, *Ann Surg* 93 30, 1931

According to Deelman, with Denmark and Switzerland, Holland, has the "doubtful privilege" of being at the head of a series of countries with the highest mortality rate from cancer. In his investigation on the heredity of cancer, the Dutch scientist asked the following question, In general, does cancer occur more frequently in the family of patients with cancer than in any other family in which there are at the moment no patients with cancer? The study is based on 250 gastric cancers collected over a period of three years.

Deelman's conclusions are as follows: 1. In a series of families of patients with cancer cancer occurs more frequently than in any other series of families. 2. The surplus of cancer in the family of patients with cancer always accumulates in certain distinct families. 3. There is a large group of patients with cancer in whose family cancer is absolutely not more frequent than agrees with the "normal" chance of dying of cancer. 4. Hereditary influences are evident only in a small category of cases of cancer. 5. So far as can be judged from the material, there is no difference between the groups alluded to in 3 and 4 in regard to the localization of the primary tumor.

B. M. FRIED

THE INTERRELATION BETWEEN HEREDITARY PREDISPOSITION AND EXTERNAL FACTORS IN THE CAUSATION OF CANCER MAUD SLAYE, *Ann Surg* 93 40, 1931

During 14,000 necropsies, 1,301 neoplasms were found, of these 51 arose under observation at the sites of recorded gross trauma. In addition to these mice, in which there was involvement in external sites, there were 3 male mice in which tumor of the liver developed, each of which had been wounded and deeply bruised subcutaneously, immediately over the location of the tumor of the liver. It is interesting that within a stock of "noncancerous" strains identical gross traumas have occurred as frequently as in the cancerous strains without in any case leading to the formation of a neoplasm.

The article, which is the first of a series to be published, is illustrated with typical protocols. Slye concludes that in her material hereditary predispositions and external gross traumas were the interrelated causes of the occurrence of cancer.

B M FRIED

EPITHELIAL METAPLASIA AND ITS RELATIONSHIP TO TUMORS G ROUSSY and C OBERLING, *Ann Surg* **93** 90, 1931

The opinion of the authors is that metaplasia should not be regarded as a pre-cancerous lesion. It is common knowledge that metaplasia of the epithelium often occurs in organs following the development of a cancer. Thus in the gallbladder and in the uterus metaplasia of the epithelium is exceedingly rare in normal conditions, whereas metaplastic (heterotopic) tumors are not so uncommon. From the practical point of view, the interpretation of epithelial metaplasia should vary according to the organ involved. Whereas in the bronchus, the pancreas and the epididymis metaplasia does not signify imminent cancerization, in the uterus the finding of islands of heterotopic (malpighian) tissue is often a sign of a condition of cancerization.

B M FRIED

EPIDERMOID CARCINOMA IN SEBACEOUS CYSTS EVERETT L BISHOP, *Ann Surg* **93** 109, 1931

The development of carcinoma in the wall of a "wen" is probably less rare than is commonly believed. A good discussion of these cancers is given, with illustrative photomicrographs.

B M FRIED

INTRACRANIAL CARCINOMATOUS METASTASES R MEAGHER and L EISENHARDT, *Ann Surg* **93** 132, 1931

Of 1,850 verified intracranial tumors, 57 (or 3 per cent) were metastatic, and of these 44 (23 per cent) were carcinomatous. The average age of the patients with intracranial metastases of the breast was 51 years, the oldest being 65, and the youngest 30. The onset of the intracranial signs after the primary focus in the breast averaged over three and one-half years, the interval ranging from three months to twelve years. The course from the appearance of intracranial symptoms was rapid, fatality ensuing on an average in six months, and operative intervention was survived on an average for six weeks, the longest period being five months.

B M FRIED

THE GENETIC NEOPLASTIC RELATIONSHIPS OF HODGKIN'S DISEASE, ALEUKEMIC AND LEUKEMIC LYMPHOBLASTOMA AND MYCOSIS FUNGOIDES ALDRFD SCOTT WARTHIN, *Ann Surg* **93** 153, 1931

The presentation is based on 100,000 specimens examined between the years 1895 and 1927. Warthin is of the opinion that Hodgkin's disease is a neoplasm, being related genetically to the lymphoblastomas, of which both the aleukemic and the leukemic forms (mycosis fungoides) are identical pathologically. They all take their origin from perivascular reticulo-endothelium, or the maternal lymphoblasts of the lymphoid tissues of the body. They show true infiltrations and metastases. In their cell types and architecture they follow definite patterns which cannot be explained on the basis of an inflammatory reaction.

B M FRIED

STUDIES IN HODGKIN'S DISEASE ELSIE S L'ESPERANCE, *Ann Surg* **93** 162, 1931

The granulomatous character of the typical lesions speaks in favor of the conception that Hodgkin's disease is tuberculous. The author relates experiments to the effect that the avian tubercle bacillus is most likely the causative agent of

the disease. Experiments on the inoculation of chickens with an emulsion of lymph nodes from two patients with established Hodgkin's disease are described. The author is of the opinion that if animal inoculations were pursued consistently along the lines of recent investigations it would determine the tuberculous nature of at least one form of Hodgkin's disease.

B. M. FRIED

SUSCEPTIBILITY AND RESISTANCE TO TAR CANCER. J. MAISIN, *Ann Surg* **93** 180, 1931

Maisin is of the opinion that cancer caused by tar results not only from local irritation, but from a general intoxication of the organism as well. Mineral salts, such as magnesium and copper, when given in convenient doses, are capable of delaying the appearance of cancer and of lowering the percentage of induced tumors. Salts of radioactive metals have an opposite effect. Diet can influence the appearance and evolution of cancer caused by tar. Thus a diet of liver accelerates the evolution of cancer caused by tar. Preceding closely the development of cancer caused by tar and during its evolution the metabolism of fats is deficient and the variations of the cholesterolemia are marked. The same variations are to be noticed after repeated injections of ionium.

B. M. FRIED

CARCINOMATOUS GASTRIC POLYP. T. GRIER MILLER, E. L. ELIASON and V. W. M. WRIGHT, *Arch Int Med* **46** 841, 1930

Carcinomatous polyp of the stomach is more frequent than has been generally believed, having been found in 35 per cent of all the cases of intragastric polyp that we have studied adequately (eight of twenty-three), and both the history and the pathologic data suggest that it usually originates in polyp of a benign nature. The benign intragastric polyps that show this tendency to malignant change are usually of an adenomatous construction. Most of the patients showing such malignant change are males (83 per cent), and the age incidence is the same as for mural gastric cancer. The symptoms are those of any malignant gastric lesion with, in addition, those of the two other common consequences of gastric polyp—intermittent pyloric obstruction and hemorrhage. The hemorrhage may be frank or occult, it not infrequently leads to an erroneous diagnosis of primary anemia (three of our eight personal cases). Consequently, gastric polyp should be considered in all cases of unexplained anemia. Roentgenologic study alone often makes the diagnosis of gastric polyp, and malignancy may be suspected on the basis of the clinical picture. Gastric polyp may be overlooked at operation, and special procedures, including gastrotomy and exploration of the interior of the stomach with a gastroscope, are indicated when any clinical suspicion of a polyp exists or when a suspected ulcer is not found. All gastric polyps, when demonstrated, deserve the radical surgical treatment commonly employed in cases of known or suspected gastric carcinoma.

AUTHORS' SUMMARY

CARCINOMA OF THE STOMACH IN A SEVENTEEN YEAR OLD GIRL. A. MARBLE, *Bull Johns Hopkins Hosp* **48** 39, 1931

An adenocarcinoma with metastases in the regional lymph nodes, removed at operation from a girl of 17 years, is described. The duration from the onset of symptoms was thirty-three months. Partial gastrectomy was made twenty-two months before death.

PRINCIPLES OF PROGNOSIS IN CANCER. WILLIAM C. MACCARTY, *J. A. M. A.* **96** 30, 1931

I think it may be said scientifically that any system of microscopic grading of cancer should not alone be of accurate clinical value without taking many other factors into consideration. Furthermore, any system which merely states that

a certain percentage of patients with certain grades live a certain length of time does not necessarily furnish data for any specific case. In other words, there is no criterion by which one can state that a given case belongs in the favorable or unfavorable percentage. Moreover, the wise and successful practitioner of the art of medicine will certainly take all possible factors into consideration in making a clinical prognosis.

These practical clinical generalizations should not inhibit or prohibit pure scientific studies of possible factors which may or may not be indexes of behavior rather than prognosis in cancer. Perhaps these indexes might be of clinical value in the future, but at present all grading of cancers should be considered in the investigative or experimental stage.

AUTHOR'S SUMMARY

THE DEVELOPMENT OF CANCER IN SCARS FROM BURNS N. TREVES and G. I. PACK, Surg. Gynec. Obst. **51** 749, 1930

Epidermoid carcinoma developed in 2 per cent of 2,465 patients with carcinoma of the skin, and in 0.3 per cent, in which, the tumors were of the basal cell type, the tumor originated on skin subjected to thermal injuries. This latter type occurred in instances wherein the burn was sufficiently superficial to spare the hair follicles and sweat glands. The age of the scar is more important than the age of the person, because this variety of cancer may occur in young people if the scar has existed for a long time, as from infancy or childhood. Scars accompanied by ulcers, fistulas, rhagades and adhesions establish an abnormal relation between epithelial and connective tissues and predispose to carcinomatous formation. Malignant changes in these scars are often multiple and may invade the surrounding scar, muscles, tendons and bones and extend by direct growth along the deep fascial planes. The lesion may be flat, indurated, infiltrative, ulcerative or everted, assuming a papillary character. In the early stage, the carcinomatous process appears in the scar as an enlarging warty or scaling papule or in the form of a diffuse tumefaction, either of which may undergo ulceration in time.

RICHARD A. LIFVENDAHL

MIXED TUMORS OF THE KIDNEY IN INFANCY AND CHILDHOOD H. L. KRETSCHMER and W. G. HIBBS, Surg. Gynec. Obst. **52** 1, 1931

Seventeen embryonal renal tumors are described. The tumor was bilateral in two cases. The kidney takes no part in the formation of the tumor. Glandular elements are always present, smooth and striated muscle, cartilage, fat and elastic, fibrous and myxomatous tissue are nearly always present. Embryonic tubules embedded in a heterogeneous matrix are the most conspicuous features. Metastases in the liver duplicate remarkably the typical new tubule formation, being arranged singly or in clumps.

RICHARD A. LIFVENDAHL

CLASSIFICATION OF TUMORS W. F. HARVEY and T. D. HAMILTON, Edinburgh M. J. **37** 609, 1930

The classification advocated is of one into families, general, species and varieties, after the manner adopted in biology. Such a classification must conform to the ordinary rules of logical subdivision and naming. Especially is the error of a mixed basis for the formation of classes to be avoided and that of combining description with the genus, species or binomial terminology. The designations blastoma and cytoma may advantageously be substituted for malignant and non-malignant tumors and the time-honored names carcinoma and sarcoma may be abolished altogether. It is also recommended to do away with the designation papilloma in either a generic or a specific sense, papillary character is excluded from the name and relegated to the position of a descriptive character. Locality, tissue type and malignancy form the basis for the nomenclature recommended, and an attempt is made to put the principles advocated into practice by the presenta-

tion of a tentative classification of tumors. It is recognized that any such classification or a similar classification must first receive approval before it could ever be generally adopted.

AUTHORS' SUMMARY

THE IMMUNOLOGICAL RELATIONSHIPS OF FOWL TUMOURS WITH DIFFERENT HISTOLOGICAL STRUCTURE C. H. ANDREWES, *J. Path. & Bact.* **34** 91, 1931

Six fowls bearing the slowly growing fibrosarcoma MH₁ have been found to have in their serum neutralizing properties active against filtrates of the Rous sarcoma no. 1. These serums would also neutralize filtrates of endothelioma MH₂ of the fowl. Similar neutralizing properties were found in the serum of only two of thirty-eight supposedly normal fowls. In birds bearing Rous sarcomas or MH₂ endothelioma, neutralizing antibodies may develop against the Rous virus in their serums, but the appearance of the neutralizing properties is far from constant.

AUTHOR'S SUMMARY

HISTOLOGY AND HISTOGENESIS OF A FILTRABLE ENDOTHELIOOMA OF THE FOWL J. A. MURRAY and A. M. BEGG, *Ninth Sc. Rep. Investigations of Imp. Cancer Research Fund*, 1930, p. 1

The tumor is transmitted by cell-free material. The cells of the new tumor are cells of the animal injected; the new tumor is a primary growth in the sense that cancer caused by tar is a new primary growth. The first indication of new growth is an accumulation of lymphocytes in the inoculated area which increase quickly in size and appear like macrophages. The macrophages proliferate by mitosis, become amoeboid and throw off granular or vesicular portions of cytoplasm. Apparently in response to the setting free of a tumor agent the susceptible cells of the area start to proliferate. It looks as if the tumor agent develops and increases in the macrophages. This conception is of interest in view of the mononuclear reaction in carcinoma.

CONGENITAL RHABDOMYOMA OF THE HEART L. BERGER and A. VALLEE, *Ann. d'anat. path.* **7** 797, 1930

Multiple nodules of striated muscle, varying in size up to that of a small cherry, were found in the myocardium of a boy, aged 2 years. The tumors are regarded as congenital. The authors found forty-one cases of congenital rhabdomyoma recorded in the literature.

H. S. THATCHER

ETIOLOGY OF TUMORS M. MARULLAZ, *Ann. de l'Inst. Pasteur* **45** 443, 1930

Analogies are drawn between the spontaneous malignant growth and those produced in the laboratory. A general discussion is presented, dividing tumors on the basis of cause as traumatic, spontaneous and functional (placental, etc.). The great importance of the nerve elements in the formation of neoplastic tissue is stressed. A note reports the death of the author some days after the receipt of this paper.

M. S. MARSHALL

THE GRAFTING OF HUMAN CANCER ON THE CHIMPANZEE J. TROISIERS, *Ann. de l'Inst. Pasteur* **45** 660, 1930

After numerous failures, I have once succeeded in transplanting a melanoma of the eye from a human being to a chimpanzee. Histologic examination has shown that the cellular elements of the transplanted melanoma were alive with their nuclei intact and their inclusions of melanin unmodified; the neoplastic tissue was compensated, and there was no adjacent lymphoconjunctival reaction. A certain local dissemination of the melanoma is clearly recognizable in the slides, but there were no metastases. If it is difficult to admit unreservedly that I have

inoculated a cancer disease of man to the anthropoid ape, it can nevertheless be said unequivocally that the heteroplastic graft of human neoplastic cells has been accomplished with the chimpanzee. In this sense it may be stated that the melanoma of man may be transferred to the chimpanzee.

AUTHOR'S CONCLUSIONS

MIXED SQUAMOUS AND CYLINDRIC CELL CARCINOMA OF THE GALLBLADDER W ROESSIGER, Beitr z path Anat u z allg Path **85** 181, 1930

According to the author, the literature contains records of only about thirty cases of pure squamous cell carcinoma of the gallbladder. To 1927, only eight cases of mixed carcinoma composed of both squamous and cylindric epithelial cells had been described. Roessiger reports three cases of such mixed carcinoma and one of squamous cell carcinoma. The fact that many carcinomas of the gallbladder are composed of cells that are indifferent in character and neither characteristically squamous nor columnar led him to postulate the presence of indifferent basal cells, in the mucosa of the gallbladder, in the sense of Krompecher. In surgically removed noncancerous gallbladders, he found cells that he holds to be basal cells. They occur singly or in small groups, not to exceed four cells, and lie immediately beneath the columnar epithelium of the mucosa. These cells, like the basal cells elsewhere, are pluripotent. Under normal conditions they give rise to cylindric cells. Chronic inflammation and cholelithiasis cause only slight proliferation of the basal cells and only rarely lead to the formation of squamous epithelium from the basal cells. The cancer stimulus, however, causes more active multiplication of the basal cells. They may remain indifferent in morphology, or they may differentiate in two directions, leading to the formation of atypical squamous epithelium or atypical columnar epithelium. Carcinomas of the gallbladder may therefore contain squamous epithelium that has arisen, not by metaplasia of pre-existing columnar epithelium, but by differentiation of indifferent basal cells.

O T SCHULTZ

MALIGNANT TUMOR OF THE CERVIX IN AN INFANT F KOHLHAAS, Monatschr f Geburtsh u Gynak **86** 58, 1930

A malignant tumor of the cervix was noted in a child, aged 16 months, who died of bronchopneumonia. At the age of 6 months, bloody vaginal discharges were the first indications of disease, and thereafter bleeding of several days' duration recurred at intervals of three or four weeks. At autopsy, metastases were found in the para-aortic lymph glands, the liver, the right lung and the right bronchial lymph nodes. The primary tumor had perforated the right common iliac vein, which was thrombosed. The pelvic tumor growth had also compressed the bladder and ureters, so that a large bilateral hydronephrosis resulted. The tumor cells resembled epithelium, and had large, lightly stained nuclei and a large amount of cytoplasm. Some cells were spindle-shaped and resembled fibroblasts. The picture was not that of a pure carcinoma, and much less that of a sarcoma, so that a diagnosis of an immature malignant tumor was made.

GEORGE RUKSTINAT

A PECULIAR CAROTID TUMOR B BAGER, Acta chir Scandinav **66** 311, 1930

A typical carotid adenoma, the size of a hen's egg, was removed from the neck of a man, aged 23, who had a definite enlargement of the thyroid gland. The carotid tumor was situated anterior to the sternomastoid muscle and was not connected with the thyroid gland, but was attached to the carotid sheath by a vascular pedicle. About eighteen months later, a tumor weighing 190 Gm., which was identical with the first, was removed from the left lobe of the thyroid gland. Presumably, the first tumor was an atypically situated carotid new growth the metastasis of which caused the enlargement of the thyroid gland.

GEORGE RUKSTINAT

Medicolegal Pathology

TRAUMA AND SARCOMA G VILLATA, *Minerva med* **1** 989, 1930

A boy, aged 11 years, fell on his hip, and an extensive hematoma developed. Twenty-five days later a growth the size of an orange developed which had a sarcomatous structure. In the center of the tumor was a splinter of bone with periosteum.

POSTMORTEM PHYSICOCHEMICAL CHANGES OF LIVER CELLS W LAVES, *Deutsche Ztschr f d ges gerichtl Med* **16** 61, 1930

Experimental investigations regarding the physicochemical processes governing the staining of tissues, particularly in relation to the method of Pischinger, are recorded. The author proved that the staining of histologic elements depends not only on the hydrogen ion concentration of the fluids used, but on the electrostatic properties of certain tissue colloids. After death, the hepatic cells, for instance, of the central parts of the acini present tinctorial changes earlier than those on the periphery of the acinus. This interesting study should be read in the original.

E L MILOSLAVICH

CARBON MONOXIDE POISONINGS IN KITCHENS H HUG, *Deutsche Ztschr f d ges gerichtl Med* **16** 72, 1930

The author presents an analysis of six fatal cases of carbon monoxide poisoning, involving women who used a gas range for boiling laundry in a large wash boiler. A detailed technical discussion regarding the development of carbon monoxide is presented.

E L MILOSLAVICH

SUDDEN DEATH WHILE SWIMMING OR DIVING MARGULIES, *Deutsche Ztschr f d ges gerichtl Med* **16** 112, 1930

According to the author's observations on man and on animals, the drowning process lasts from four to five minutes. A rapid or sudden death is often attributed to a heart stroke or to shock. Distention of the lungs is often found, but it may also be absent. Absence of any signs of hyperaeration of the lungs does not prove that the victim did not drown. Hyperaeration indicates that the person was alive when submerged. Sudden death while the patient is submerged may be the result of the mechanical action or of direct or indirect pressure of the fluid medium or water on the cavities of the body, leading to a mechanical paralysis of the heart. The explanations are based on physiologic and anatomic considerations under various abnormal conditions.

E L MILOSLAVICH

DETERMINATION OF BLOOD GROUP ON CONVICTS W HENNEMANN, *Deutsche Ztschr f d ges gerichtl Med* **16** 126, 1930

Examination of 310 convicts has shown that there is no definite relation between the blood group and the type of delinquent. The blood groups were proportionately distributed among the dangerous criminals and the habitual and professional delinquents. Group B was not prevalent among persons who committed heinous crimes, as is asserted by other investigators.

MOVEMENTS AND OTHER ACTIONS BY PERSONS FATALLY INJURED • KARL MEIXNER, *Deutsche Ztschr f d ges gerichtl Med* **16** 139, 1930

Fractures of the bones of the lower extremities do not exclude the ability to walk. Fractures of the ribs and spine may remain unnoticed by the person injured. Concussion of the brain alone does not cause death, but produces instantaneous unconsciousness. Fat embolism of the kidneys and pancreas should be considered in cases in which death occurred slowly under a coma-like picture. In

certain rare instances, penetrating gunshot wounds of the brain will not cause an immediate collapse, and the critically injured person is able to walk and react. Injuries to the frontal lobes manifest symptoms later than those to any other cerebral area. In young persons, injuries to the head cause concussion of the brain rather than fracture of the cranial bones, which occurs more frequently in older persons. Therefore, in the latter instance, some acts by the injured person are not uncommon, while concussion with the concomitant unconsciousness eliminates any movement. Absence of swallowed blood in the stomach in instances of traumatic hemorrhages from the nasopharyngeal region, but with presence of blood in the lung (aspiration but no ingestion), proves that the unconsciousness occurred simultaneously with the injury, however one has to consider that severe traumatism to the skull and brain occasionally occur without rapidly developing unconsciousness. The author discusses gunshot injuries and stab wounds of the heart and the possibilities of their healing. In only a comparatively low percentage of cases does death occur suddenly after stabbing of the heart. Stab wounds of the ascending aorta seem to lead to a fatal end more rapidly than do those of the cavities of the heart. Experience teaches that gunshot wounds of the heart produce a sudden collapse and thus exclude any activity. This is also true occasionally of gunshot wounds of the lung. In not 1 of 185 cases of injuries to the heart produced by blunt violence was the injured person capable of action.

E L MILOSLAVICH

SUICIDE IN FAVOR OF INSURER W ELIASBERG, *Deutsche Ztschr f d ges gerichtl Med* **16** 166, 1930

An interesting case is reported of a banker who insured his life for a great sum of money and then committed suicide to favor the bank. Detailed criminopsychiatric analysis is presented as to the underlying motives for this action.

E L MILOSLAVICH

SUICIDE WITH A DEVICE FOR SLAUGHTERING ANIMALS F WALLBAUM, *Deutsche Ztschr f d ges gerichtl Med* **16** 174, 1930

The author gives a description of the instrument and the manner in which it was used. The unusual feature of the case was that the shooting device was placed on top of the head. Two similar cases have previously been described by Schoenberg. In both of the latter instances, however, the instrument was pressed against the forehead.

E L MILOSLAVICH

NETTLE STING (URTICA URENS) BURNS AS CAUSE OF DEATH E A JAKOWLEWA, *Deutsche Ztschr f d ges gerichtl Med* **16** 180, 1930

A poorly nourished, anemic and underdeveloped girl, aged 6 years, died suddenly under peculiar circumstances. The skin showed a rash that was interpreted as measles. Investigation disclosed that the foster mother, who often mistreated the girl, in order to punish her because she stole a piece of sausage, undressed her and whipped her with recently plucked nettle until she collapsed. Microscopic examination of the cutaneous rash detected innumerable nettle-stinging hairs within the reddened areas. It was assumed that death resulted from shock.

E L MILOSLAVICH

POISONOUS ACTION OF ZINC SALT SOLUTIONS R ZEYNEK and H WAELSCH, *Deutsche Ztschr f d ges gerichtl Med* **16** 184, 1930

In a case of criminal abortion the uterus was irrigated with 0.5 per cent solution of zinc chloride, death occurring one and a half hours afterward. One expert assumed that death resulted from an acute zinc poisoning. The authors deny any action of zinc and base their opinion on experimental proof, they correctly assumed that the fatal end was caused by septicemia.

E L MILOSLAVICH

RESULTS OF AUTOPSY ON EXHUMED BODIES. FERDINAND KLEMP, *Deutsche Ztschr f d ges gerichtl Med* 16 190, 1930

The postmortem observations on twenty-four disinterred and unembalmed bodies are presented in every detail, and the difficulties in correct interpretation of the changes are critically discussed. In only sixteen instances were the corpses well preserved. In disintegration of a dead body, the autolytic, decomposing and putrefactive processes must be considered separately. Autolysis embraces all of the chemical processes that ensue from liberated endocellular enzymes, leading to an autodigestion of the tissues, without any influence of micro-organisms. The decomposition is characterized by processes of oxidation and nitrification liberating heat, the high chemical compounds being transformed into simpler compositions. The putrefaction is the result of bacterial action with subsequent disintegration of tissues to simple chemical substances. The sooner after death chilling of the body occurs, the more retarded is the disintegration. Well nourished, fat bodies, a fluid condition of the blood, external wounds, septic processes, agonal invasion of bacteria, etc., are factors favoring a rapid development of disintegration. Cadaveric rigidity does not necessarily disappear with advanced putrefaction. In instances of potassium cyanide poisoning, a chemical examination is usually futile, since this poison disintegrates rapidly after death. According to the observations, the intestines resist putrefaction longer than the liver, spleen or kidneys. The non gravid uterus remains comparatively well preserved for a long time. The organs of the neck exhibit a remarkably rapid disintegration, while changes are still recognizable in the lungs and the heart. While the membranes of the brain, particularly the dura mater, disappear quite rapidly, the brain itself remains relatively longer.

C. L. MILOSLAVICH

Technical

THE BOLTZ TEST IN URINALYSIS. A. T. BRICE, JR., *Arch Int Med* 46 778, 1930

Technic (a) Place in a small glass test tube 1 cc. of the filtered or centrifugated specimen to be examined. (b) Add 0.3 cc. of acetic anhydride, preferably a brand high in aldehyde content, from a pipet, a drop at a time, with shaking. (c) Add 0.8 cc. of concentrated sulphuric acid, from a pipet, a drop at a time, with shaking. (d) Let the tube stand at room temperature under observation for five minutes.

The positive reaction is indicated by the appearance of a light lilac to deep purple color. Occasionally, in weak positive reactions the positive color may appear within the five minute period and subsequently be obliterated by the darker colors due to the reaction of other substances in the urine. Occasionally, in strongly positive reactions the positive color may not appear before the expiration of some minutes, owing to the darker colors produced immediately by the reaction of other substances in the urine. In strongly positive specimens the purple color may be so dark as to require dilution of the preparation with water in order to differentiate the purple from possible dark browns or blacks. The prescribed five minutes of the test is a valid test period, as positive specimens have been shown to hold the positive color for several hours. The test with urine is practically impossible to read by any of the artificial lights with which I have experimented up to the time of writing.

The positive reaction is thought to be due to an amino-acid, presumably tryptophan, eliminated in the urine. The test may prove to be more valuable than the test for albumin to demonstrate early or latent conditions of the kidney. There is also evidence that the positive Boltz reaction in urine is of significance in nervous and mental cases and in shock.

ERYTHROCYTE SEDIMENTATION TEST IN TUBERCULOSIS ANDREW L. BANYAI and SYLVIA V. ANDERSON, *Arch Int Med* **46** 787, 1930

A study of the sedimentation test, a modification of the Westergreen method being used, is reported in 2,000 patients. It is shown conclusively that the rate of sedimentation cannot be used for the diagnosis of tuberculosis. The main factor influencing the sedimentation rate is the toxicity of the infection and not so much the extent of the lesion. The greatest merit of the test lies in its value as an indicator of the course of the disease, an increase in the rate indicates an advance in the disease or the onset of some complication, while a retardation in the rate points to improvement.

J. N. PATTERSON

A NEW DEMONSTRATION OF HORTEGA CELLS ROBERT R. DIETERLE and META NEUMANN, *Arch Neurol & Psychiat* **24** 1154, 1930

The authors use to great advantage Kubie's formulas for silver staining which they recommend instead of the methods of Bielschowsky, del Rio-Hortega, Achucaro and Perdrau. The method for demonstrating Hortega cells, as described, is as follows:

Pieces of brain tissue, from 2 to 3 mm thick, are fixed in ammonium nitrate, 10 Gm., formaldehyde (Merck's Blue Label), 70 cc., and distilled water, 430 cc. Frozen sections, 20 microns thick, may be made after from twenty-four hours to three or eight days of fixation. A dozen sections are left for ten minutes in 50 cc. of distilled water plus 5 drops of ammonium hydroxide. The sections are rinsed singly in 100 cc. of distilled water and transferred to Kubie's ammoniacal silver carbonate solution, which consists of the following elements: (809 cc. of 28 per cent ammonium hydroxide diluted to 100 cc., 3.2 Gm. of sodium carbonate dissolved in distilled water up to a final volume of 100 cc., 10.2 Gm. of silver nitrate dissolved in distilled water up to a volume of 100 cc., 10 cc. of the latter is put in a 100 cc. volumetric flask, and the diluted ammonia solution is added, it should be shaken vigorously between additions toward the end-point, then 10 cc. of the sodium carbonate solution is added to make up a final volume of 100 cc., in 50 cc. of this solution a dozen sections are placed at room temperature in the dark.) Reduction is done by formaldehyde (Merck), 10 cc., pyridine, 10 cc., mastic, 10 cc. (10 per cent absolute alcoholic), distilled water sufficient to make 100 cc. To 50 cc. of this developer 1 cc. of 1 per cent of hydroquinone solution is added. Development occurs almost immediately. The mastic is dissolved in 96 per cent alcohol, the section is blotted on the slide, cleared in 10 per cent phenol-xylene and mounted in balsam. This method brings out the entire structure of Hortega cells, it shows more of their protoplasmic structure than "any method yet devised." For further minor details the article itself, as well as Kubie's contributions (*Arch Neurol & Psychiat* **19** 888, 1928, **22** 135, 1929), should be consulted.

GEORGE B. HASSIN

Society Transactions

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, March 9, 1931

JOSEPH A CAPPS, *President, in the Chair*

PRIMARY, ISOLATED LYMPHOGRANULOMATOSIS OF THE STOMACH HARRY A SINGER

Pathologists have known for many years that lymphogranulomatosis may originate not only in lymph glands, but in any viscus containing lymphoid tissue. The occurrence of primary lesions in the spleen, liver, bone marrow and lungs has attracted little surgical attention because the diagnosis and surgical extirpation of localized lesions is difficult. Primary lesions of the gastro-intestinal tract and particularly those of the stomach manifest themselves promptly, diagnosis is not difficult, and surgical removal is relatively safe.

In the literature seven cases of primary, isolated Hodgkin's disease of the stomach are reported. The preoperative diagnosis was either carcinoma or ulcer, and in all, gastric resection was performed. Five patients recovered and remained well, one died after two years, and the seventh died of obstruction at the stomach a month after operation. No other lesions of lymphogranulomatosis were found post mortem, but microscopic examinations of the various organs are not mentioned. The eighth report of isolated Hodgkin's disease of the stomach, the second in this country, is unique in that a careful gross and microscopic post-mortem examination of the tissues failed to disclose lesions elsewhere in the body.

The clinical diagnosis of isolated lymphogranulomatosis of the stomach is hardly possible in the present state of knowledge. The systemic manifestations are generally absent when the lesion is still in the operable stage. The presence of a soft, flat, infiltrating tumor limited strictly to the distal portion of the stomach, associated with a number of large, succulent, isolated, adenoid-like glands, should suggest the possibility of lymphogranulomatosis. The final diagnosis is made by histologic examination. Inoperable tumors of the stomach should be examined microscopically.

Even in cases in which careful exploration fails to demonstrate granulomatous tissue other than that removed, the prognosis should be guarded. Gross lesions in inaccessible regions and minute foci in the structures examined during operation may escape detection. In cases in which the extent of involvement precludes resection, the patient should be given roentgen therapy.

The complete report will be published in the *Archives of Surgery*.

DISCUSSION

R. H. JAFFE The term lymphogranulomatosis may not be suitable for these lesions. Perhaps malignant granuloma would be better.

E. F. HIRSCH The implication that all of these lesions are of the character of Hodgkin's disease may be extreme, because there occur in the intestinal tract lesions of granulation tissue which in some respects resemble those of Hodgkin's disease and yet etiologically are different, as, for example, the chronic changes in the wall of the bowel which occur following traumatic evulsion of the mesentery.

REACTION OF THE BONE MARROW IN EXPERIMENTALLY INDUCED THROMBOCYTOSIS FRANCIS D GUNN

This paper will be published in full in a future issue of the ARCHIVES.

THE EOSINOPHIL RESPONSE IN PERSONS GIVING POSITIVE SKIN REACTIONS TO INJECTIONS OF DICK TOXIN STUART L VAUGHAN

In a general study of the reactions of bone marrow a method for gaining new information on the pathogenesis of scarlet fever has presented itself. In this

disease an early and persistent eosinophilia of the blood has long been recognized as constant. This is also one of the prominent characteristics of allergy, and has led a number of investigators to conclude that allergy has an important role in the manifestations of scarlet fever. Recent developments have stimulated interest in the subject.

The experiment consisted of making differential blood counts before and at intervals following the injection of immunizing doses of Dick toxin into a group of eleven student nurses with positive skin reactions, and analyzing the response of the eosinophil leukocytes. The reactions of the skin varied from weakly to strongly positive. The average initial content of eosinophil leukocytes was 0.9 per cent. In every case a decided rise was observed during the course of the injections. The smallest increase was 150 per cent and the greatest was 950 per cent above the normal average. The average increase was 260 per cent. The time of appearance of the eosinophilia varied. In 54 per cent, a marked increase was present within four hours. In two nurses, it was not noted until after the third injection. In the two others with very strong reactions to the Dick test, the eosinophilia was coincident with the appearance of a rash.

These results raise a number of interesting considerations. An increase in the circulating eosinophil leukocytes immediately following the injection of this streptococcus culture-filtrate is contrary to results with filtrates of other bacterial cultures. If eosinophilia of the blood is an allergic response, these results support the contention that a high percentage of persons with positive Dick reactions are sensitized to some constituent of the injected material. That the injections themselves may produce an allergic state or augment one already existing is supported by the delayed increase in eosinophil leukocytes in two cases and a late appearance of maximum increase in others. Evidence is present that the positive Dick reaction may not be allergic. In the two nurses giving the strongest skin reactions, the eosinophilia was not immediate, although susceptibility to the filtrate was shown by the prompt appearance of an erythema. In two other nurses the reaction of the blood appeared only after three injections. The rash, which has been mentioned as the cause of the eosinophilia, was present in but two cases. It may have no causal relationship. Possibly both reactions were the result of the same stimulus. If so, eosinophilia is more easily elicited than a reaction of the skin.

PHILADELPHIA PATHOLOGICAL SOCIETY

Regular Meeting, March 12, 1931

BALDUIN LUCKE, *President, in the Chair*

Dr. Warren H. Lewis, of the Carnegie Institution of Washington and Johns Hopkins University, presented moving pictures of tissue cultures of human and mammalian tumor cells, endothelium, capillaries, blood cells and macrophages.

The Annual Conversational Lecture, April 17, 1931

BALDUIN LUCKE, *President, in the Chair*

CELLULAR REACTIONS TO FRACTIONS ISOLATED FROM TUBERCLE BACILLI FLORENCE R. SABIN, M.D.

In following the blood of rabbits infected with large intravenous doses of bovine tubercle bacilli, it has been found that an increase in lesions in the tissues has been reflected by a rise in monocytes in the peripheral blood. These monocytes are often stimulated even to the epithelioid type. On the other hand,

increased resistance on the part of the animal has been correlated with a rise in lymphocytes. These two factors may be expressed in a monocyte/lymphocyte ratio.

Fractions isolated from the acid-fast strains of organisms have given valuable material for testing these theses and for studying the relationships of monocytes to clasmatocytes or macrophages. Tubercle bacilli have been grown under standard conditions by the H. K. Mulford Company, and the lipoidal extracts have been analyzed by Dr. R. J. Anderson of Yale University. The alcohol-soluble lipid, or phosphatide, produces typical tubercular tissue composed of epithelioid cells and epithelioid giant cells. This action is due to the presence of a new liquid saturated fatty acid, which Dr. Anderson has named phthioic acid.

The immediate reaction to the phosphatide is shown by the relatively immature cells of the milk spots. These cells phagocytose the phosphatide and seem to break it into finer and finer particles, until a typical epithelioid type of cell is reached. This reaction is slow, and the epithelioid cell persists a long time. This type of intracellular reaction is in contrast to clasmatocytic activity. The injection of the tuberculopolysaccharide intraperitoneally is always followed by an emigration of leukocytes that seem to be damaged, for they are phagocytosed by the macrophages and completely disintegrated in about forty-eight hours. Thus, however closely monocytes and clasmatocytes are related, there are two types of cellular activity toward phagocytosed material that may be termed monocytic and clasmatocytic.

The chloroform-soluble material also contains some of the specific phthioic acid, together with an unsaponifiable material, which is intensely acid-fast. This material produces as great a cellular reaction as the phosphatide, but of undifferentiated connective tissue cells. The smooth avian organism dissociated by Dr. S. A. Petroff has relatively little of the wax, for it is but slightly acid-fast and produces a type of tuberculosis that may be called the pure phosphatide disease.

Experiments to test validity of the theory of the relationships of the two strains of cells, monocytes and lymphocytes, to resistance in tuberculosis are under way. An increase in epithelioid tissue induced by the phosphatide has been followed by lowered resistance to bovine infection in rabbits. Experiments testing the effects of increasing lymphocytes are being made at the present time.

Book Reviews

A TEXT-BOOK OF MEDICAL JURISPRUDENCE AND TOXICOLOGY By JOHN GLAISTER, M D (GLAS), D P H (CAMB), F R S E, Professor of Forensic Medicine in the University of Glasgow, etc In Collaboration with John Glaister, Jr, M B, Ch B (Glas), M D (Hons) (Glas), D Sc (Glas), Barrister-at-Law, Inner Temple, London, Professor of Forensic Medicine in the University of Egypt, Cairo, etc Fifth edition Price, \$8 50 Pp 954, with 132 illustrations and seven plates New York Wilham Wood & Company, 1931

This book is divided into two sections medical jurisprudence and toxicology Under medical jurisprudence are chapters on definitions and scope, medical evidence, personal identity of living and dead in its medicolegal bearings, death in its medicolegal relations (several chapters occupying more than 200 pages), blood stains, medicolegal relations of sexual functions, infanticide, rape, states of insensibility and lunacy in its medicolegal aspects These matters are presented thoroughly in the light of the laws and customs of Scotland and England and on the basis of a rich personal experience Many interesting and illustrative cases are cited, with much detail In the consideration of sudden death, the rôle of embolism is not stressed sufficiently The various forms of meningeal hemorrhage do not receive adequate attention The use and value of blood grouping in the identification of persons and of the source of blood stains as well as in the settlement of questions of parentage are not even mentioned The illustrations in this sections are mostly of gross appearances, the quality of the illustrations is only fair, figures 109 and 117 are worthless

The section on toxicology occupies 250 pages It covers the ground thoroughly The poisons, as well as the circumstances under which various poisonings may take place and their symptoms and the resulting anatomic changes, are described

This is the fifth edition of the book, "carefully prepared and brought up to date" Of the new matter in this edition, may be mentioned workmen's compensation acts respecting industrial diseases, national insurance acts, dangerous drugs acts, therapeutic substances act and a separate legal index The senior author has been a teacher of forensic medicine for forty-eight years, and during most of that period he has been engaged in "medico-legal practice for the Crown" The book reflects well the status of forensic medicine and its workings in England and Scotland It carries with it a certain old-fashioned air of finality, and it is a vast storehouse of medicolegal information, the fruit of years of careful practical work It will be of interest to those who are concerned with the proper application of medical knowledge in the administration of justice

TECHNIK DER MIKROSKOPISCHEN UNTERSUCHUNG DES NERVENSYSTEMS By PROF DR W SPIELMEYER Fourth edition Price, 11 80 marks Pp 168 Berlin Julius Springer, 1930

The progress in any science can be measured more or less accurately by the advancement of its technic, and the fourth edition of Spielmeyer's laboratory guide, which is probably the most extensively used handbook of neuropathologic methods, indicates the comprehensive manner in which the nervous system is now examined Most of the additions to the previous edition, while not new in the science of neuropathology, are new in the German understanding of that science, for chief among these additions are technical methods from the Spanish school which have been brought into prominence outside of Spain by the American workers Penfield and Globus In fact, the book is more international than its previous editions

The order in which the material is presented, as in the previous editions, goes more or less hand in hand with the manner in which the nervous system is prepared and examined. An introduction explaining the principles of fixation, embedding and cutting and the preparation of certain general chemicals, such as hematoxylin, precedes the more specific parts. The fine hematoxylin of Ehrlich seems to be omitted from, and Meyer's hemalum added to, the old list.

In the methods of staining the nerve cells, several of the less desirable methods have been omitted, as has the polychrome methylene blue for the medullary sheath. Marchi's chromosmium method has been removed from its place among the stains for the medullary sheath and has been placed with methods for studying the products of disintegration.

The chief changes are in the technic of staining glia, as mentioned, Anderson's method and several modifications of Hortega's method by Penfield, Globus and Kanzler have been added, while several of the less specific methods have been omitted.

In the study of the products of disintegration, of deposits and of the histochemical aspects, one finds a new fat stain, sudan-orange, von Braunmühl's silver method for senile plaques, and a new oxydase reaction, while several methods of staining frozen sections in order to detect spirochetes and a method of staining to detect Negri bodies improve the chapters on micro-organisms.

HANDBOOK OF PROTOZOOLOGY. By RICHARD ROXSABRO KUDO, D Sc, Assistant Professor of Zoology, University of Illinois. Price, \$5.50. Pp 451, with 175 etchings containing 1,463 figures. Springfield, Ill. Charles C. Thomas, 1931.

In presenting this "Handbook of Protozoology" the author has probably supplied a long-standing need. As suggested in the preface, the study of the protozoa as a group is becoming more and more widespread in universities and colleges. The need for an introductory volume dealing with the biology of the protozoa in general and giving adequate figures of representatives of the various groups has apparently been supplied.

The introductory chapter deals with general points of morphology, as well as the relationship of protozoology to the biologic sciences as a whole. This chapter also contains a good review of the history of protozoology. The next two chapters contain discussions of the morphology and physiology of the protozoa, considering structure, reproduction, etc. The following thirty odd sections, almost the entire book, are devoted to classification and brief discussions of the various genera, species, families, etc., throughout the entire protozoan group. Representative members of the groups are pictured, and these figures have been generously supplied. It is in these chapters that the real worth of the book lies. There are many monographs on the various taxonomic groups, but this contribution is unique in that it gives in concise fashion a consideration of each division of the entire group, from the flagellates through *Sarcodina* and *Sporozoa* to the ciliates. The free and parasitic forms are given equal stress. The book is appended by a rather brief consideration of the collection, cultivation and observation of protozoa.

The illustrations deserve further comment. It is stated by the author that they have all been redrawn especially for the work. They are dependable representations of the forms, and credit is due for the quality of their execution, which greatly enhances the value of the book. The make-up, as well as the clarity with which the figures have been reproduced, contributes to the formation of a volume with a pleasing appearance.

Books Received

A TEXTBOOK OF LABORATORY DIAGNOSIS WITH CLINICAL APPLICATIONS FOR PRACTITIONERS AND STUDENTS By Edwin E Osgood, M A, M D, Assistant Professor of Medicine and Biochemistry, Director of Laboratories, University of Oregon, School of Medicine, Portland, Ore, and Howard D Haskins, M D, Professor of Biochemistry, University of Oregon, School of Medicine Price, \$5 Pp 475, with 26 illustrations Philadelphia P Blakiston's Son & Company, 1931

THE DIVISION OF LABORATORIES AND RESEARCH OF THE NEW YORK STATE DEPARTMENT OF HEALTH A SHORT ACCOUNT OF ITS HISTORY AND PRESENT THE PHYSICIAN OF THE DANCE OF DEATH A HISTORICAL STUDY OF THE

STATUS By A B Wadsworth, M D, Director Albany 1931

EVOLUTION OF THE DANCE OF DEATH MYTHS IN ART By Aldred Scott Warthin, Ph D, M D, LL D, Professor of Pathology and Director of the Pathological Laboratories in the University of Michigan, Ann Arbor, Mich Price, \$7 50 Pp 142, with 92 illustrations New York Paul B Hoeber, Inc, 1931

FOOD POISONING AND FOOD-BORNE INFECTION By Edwin Oakes Jordan, Chairman of the Department of Hygiene and Bacteriology, The University of Chicago Price, \$2 50 Pp 286 Chicago The University of Chicago Press, 1931

NOGUCHI By Gustav Eckstein Pp 418, with illustrations Price, \$5 New York Harper & Sons, 1931

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